FUSED AZOLE-PYRIMIDINE DERIVATIVES

DETAILED DESCRIPTION OF INVENTION

Technical Field

The present invention relates to novel fused azolepyrimidine derivatives, processes for preparing them and pharmaceutical preparations containing them. The fused azolepyrimidine derivatives of the present invention exhibit enhanced potency for phosphotidylinositol-3-kinase (PI3K) inhibition, especially for PI3K-γ inhibition and can be used for the prophylaxis and treatment of diseases associated with PI3K and particularly with PI3K-γ activity.

More specifically, the fused azolepyrimidine derivatives of the present invention are useful for treatment and prophylaxis of diseases as follows: inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis, and Graves' disease, cancer, myocardial contractility disorders, heart failure, thromboembolism, ischemia, and atherosclerosis.

The compounds of the present invention are also useful for pulmonary hypertension, renal failure, cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, diabetes and focal ischemia, since the diseases also relate to PI3K activity in a human or animal subject.

BACKGROUND ART

Signal transduction pathways originating from chemoattractant receptors are considered to be important targets in controlling leukocyte motility in inflammatory

diseases. Leukocyte trafficking is controlled by chemoattractant factors that activate heterotrimeric G-protein coupled receptors (GPCRs) and thereby trigger a complex variety of downstream intracellular events. Signal transduction at one of the pathways, that results in mobilization of intracellular free Ca^{2+}, cytoskeletal reorganisation, and directional movement depends on lipid-derived second messengers produced by phosphoinositide 3-kinase (PI3K) activity [1,2].

PI3K phosphorylates the D3-hydroxyl position of the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2) to yield phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P_3). Based on substrate specificity and protein structure, the PI3K family comprises three classes [4-6]. Of particular interest in leukocyte migration are class I PI3Ks, which are all involved in receptor-induced inflammatory cellular responses and are further divided into the subclasses IA (p110α, β, δ) and IB (p110γ).

Class IA enzymes (p110α, β, δ) associate with a p85 adapter subunit, which contains two SH2 domains, to form a heterodimeric complex. This complex is able to recognize phosphotyrosine YxxM motifs, resulting in association with receptor tyrosine kinases and subsequent activation of the enzyme through receptor tyrosine kinases [1, 2]. The class IA subtypes are considered to be associated with cell proliferation and carcinogenesis. The IA subtypes bind to activated ras oncogene, which is found in many cancers, to express their enzyme activity. It has also found that both p110α and β play important roles in human cancer growth [3].

Class IB (p110γ) enzyme, whose expression is largely confined to leukocytes, is activated by the G protein βγ complex, and functions downstream of seven transmembrane chemoattractant receptors [7-9]. The p101 adapter protein, which bears no resemblance to any other known protein, is essential for the G protein βγ responsiveness of the p110γ (PI3Kγ). [10-12].

Recent studies in mice lacking functional PI3Kγ (PI3Kγ-/- mice), which were viable, fertile, and displayed a normal life span in a conventional mouse facility, have revealed that neutrophils are unable to produce PtdIns(3,4,5)P_3 when stimulated with GPCR agonists such as fMLP, C5a or IL-8. This demonstrates that PI3Kγ is the sole PI3K that is coupled to these GPCRs in these cells [13-16]. Moreover, PtdIns(3,4,5)P_3-dependent activation of protein kinase B (PKB) was also absent in those neutrophils, while PKB could still be activated by GM-CSF or IgG/C3b-coated zymosan via either p110α, β or δ. At the same time, G-protein-mediated responses such as PLCβ activation were intact. PI3Kγ-/- mice showed impaired thymocyte development and increases in neutrophil, monocyte, and eosinophil populations [14]. Furthermore, neutrophils and macrophages isolated from PI3Kγ-/- mice exhibited severe defects in migration and respiratory burst in response to GPCR agonists and chemotactic agents [14,16]. Expression of PI3Kγ was also examined in transgenic mice expressing green fluorescence protein (GFP) under the control of the endogenous PI3Kγ promoter. GFP was detected in spleen and bone marrow cells, and neutrophils, suggesting that the expression of PI3Kγ is restricted to hematopoietic cells [15]. Collectively, the class IB phosphoinositide 3-kinase PI3Kγ seems to be pivotal in the control of leukocyte trafficking and accordingly the development of isotype-selective inhibitors of PI3Kγ should be an attractive anti-inflammatory strategy.

Hypertrophic responses can be initiated by PI3K signaling pathways. Currently new research was published which identify a function for PTEN- PI3Kγ pathway in the modulation of heart muscle contractility. Whereas PI3Kα mediates the alteration in cell size seen during heart hyperthrophy up to heart failure, PI3Kγ acts as a negative regulator of cardiac contractility.

PTEN is a dual-specificity protein phosphatase recently implicated as a phospho-inositide phosphatase in cellular growth signaling. The tumor suppressor PTEN is shown to dephosphorylate phosphatidylinositol 3,4,5-triphosphate (PIP3) which is an important second messenger generated specifically by the actions of PI3K. The

PTEN reduces the levels of PIP3 within the cells and antagonizes PI3K mediated cellular signaling. It is also reported that expression of dominant-negative PTEN in rat cardiomyocytes in tissue culture results in hypertrophy.

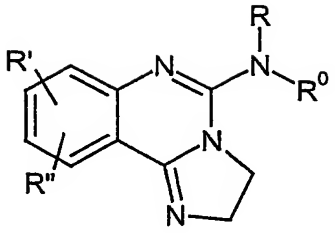
PI3Kγ modulates baseline cAMP levels and controls contractility in cells. This study also indicates that alterations in baseline cAMP level contribute to the increased contractility in mutant mice [17].

Therefore, this research result shows that PI3Kγ is involved in myocardial contractility and therefore the inhibitors would be potential treatments of congestive heart failure, ischemia, pulmonary hypertension, renal failure, cardiac hypertrophy, atherosclerosis, thromboembolism, and diabetes.

A inhibitor of PI3K, which is expected to block signaltranduction from GPCR and the activation of various immune cells, should have a broad anti-inflammatory profile with potential for the treatment of inflammatory and immunoregulatory disorders, [2] including asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis, and Graves' disease, diabetes, cancer, myocardial contractility disorders, thromboembolism [18], and atherosclerosis.

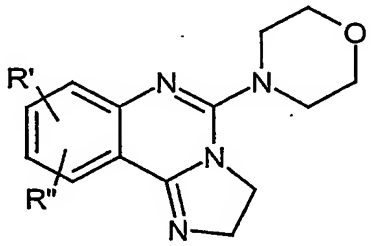
Some PI3-kinase inhibitors has been identified: wortmannin, originally isolated as a fungal toxin from *Penicillium wortmannii* [19], the closely related but less well characterized demethoxyviridin and LY294002, a morpholino derivative of the broad-spectrum kinase inhibitor quercetin [20].

US 3644354 discloses 5-substituted 2,3, dihydroimidazo[1,2-c]quinazolines represented by the general formula:



wherein R and R^0 is independently, hydrogen, lower alkyl, lower alkenyl; R' and R'' are independently, hydrogen, halogen, lower alkyl, lower alkoxy

or



as a hypotensive agents and coronary dilators

However, none of the references discloses fused azolepyrimidine such as, but not limited to, azole-quinazoline, azole-pyridopyrimidine, azole-pyrimidopyrimidine, azole-pyrimidopyridazine, azole-pyrimidotriazine, azole-pteridine, azole-pyrimidotetrazine and other derivatives having acylated amine or $-CR^5R^6-C(O)-$ ($R^5$is hydrogen or C_{1-6} alkyl and R^6 is halogen, hydrogen, or C_{1-6} alkyl) linker at the 5 or 6 position of the fused azolepyrimidine also having PI3K inhibitory activity.

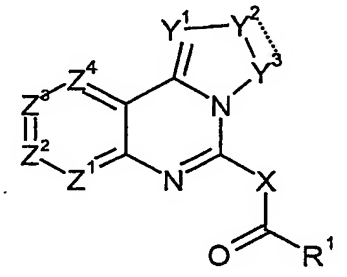
The development of a compound which is useful for treatment and prophylaxis of inflammatory, cancer and/or myocardial contractility disorders associated with PI3K activity has been still desired.

Summary of the invention

As a result of extensive studies on chemical modification of the fused azolepyrimidine derivatives, the present inventors have found that the compounds of novel

chemical structure related to the present invention have PI3K inhibitory activity and particularly have PI3K-γ inhibitory activity. The present invention has been accomplished based on these findings.

This invention is to provide novel fused azolepyrimidine derivatives of the formula (I) their tautomeric and stereoisomeric forms, and salts thereof.



wherein

X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

Chemical bond between Y^2═Y^3 represents a single bond or double bond,

with the proviso that when theY^2═Y^3 represents a double bond,

Y^2 and Y^3 independently represent CR^4 or N, and

when Y^2═Y^3 represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4;

Z^1, Z^2, Z^3 and Z^4 independently represent CH , CR^2 or N;

R^1 represents aryl optionally having 1 to 3 substituents selected from R^{11}, C_{3-8} cycloalkyl optionally having 1 to 3 substituents selected from R^{11},
C_{1-6} alkyl optionally substituted by
aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
C_{1-6} alkoxy optionally substituted by
carboxy, aryl, heteroaryl, C_{1-6} alkoxyaryl, aryloxy, heteroaryloxy or one or more halogen,
or
a 3 to 15 membered mono- or bi-cyclic heterocyclic ring that is saturated or unsaturated, and contains 1 to 3 heteroatoms selected from the group consisting of N, O and S, and optionally having 1 to 3 substituents selected from R^{11}
wherein
R^{11} represents
halogen, nitro, hydroxy, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6}acyl)amino, N-(formyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkanesulfonyl) amino, N-(carboxyC_{1-6}-alkyl)-N-(C_{1-6}alkyl)amino, N-(C_{1-6}alkoxycabonyl)amino, N-[N,N-di(C_{1-6}alkyl)amino methylene]amino, N-[N,N-di(C_{1-6}alkyl)amino (C_{1-6} alkyl)methylene]amino, N-[N,N-di(C_{1-6}alkyl)amino C_{2-6}alkenyl]amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl, C_{3-8}cycloalkyl, C_{1-6} alkylthio, C_{1-6}alkanesulfonyl, sulfamoyl, C_{1-6}alkoxycarbonyl,
N-arylamino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101}, N-(aryl C_{1-6}alkyl)amino wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101}, aryl C_{1-6}alkoxy-carbonyl wherein said aryl moiety is optionally having 1 to 3 substituents selected from R^{101},
C_{1-6}alkyl optionally substituted by
mono-, di- or tri- halogen, amino, N-(C_{1-6}alkyl)amino or N,N-di(C_{1-6}alkyl)amino,

C_{1-6}alkoxy optionally substituted by

mono-, di- or tri- halogen, N-(C_{1-6}alkyl)sulfonamide, or N-(aryl)sulfonamide,

or

a 5 to 7 membered saturated or unsaturated ring having 1 to 3 heteroatoms selected from the group consisting of O, S and N, and optionally having 1 to 3 substituents selected from R^{101}

wherein

R^{101} represents

halogen, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, N,N-di(C_{1-6}alkyl)amino-carbonyl, pyridyl,

C_{1-6} alkyl optionally substituted by cyano or mono- di- or tri- halogen,

or

C_{1-6}alkoxy optionally substituted by cyano, carboxy, amino, N-(C_{1-6} alkyl)amino, N,N-di(C_{1-6}alkyl)amino, aminocarbonyl, N-(C_{1-6}alkyl)amino-carbonyl, N,N-di(C_{1-6}alkyl)aminocarbonyl or mono-, di- or tri- halogen;

R^2 represents hydroxy, halogen, nitro, cyano, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{1-6} acyloxy, aminoC_{1-6} acyloxy, C_{2-6}alkenyl, aryl,

a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, amino, amino C_{1-6}alkyl, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, N-(C_{1-6}alkyl)carbonylamino, phenyl, phenyl C_{1-6} alkyl, carboxy, C_{1-6}alkoxycarbonyl, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)amino,

-C(O)- R^{20}

wherein

R^{20} represents C_{1-6} alkyl, C_{1-6} alkoxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, or a 5-7 membered saturated or unsaturated heterocyclic ring having 1 to 3 heteroatoms selected from the group consisting O, S and N, and optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy, oxo, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, phenyl, or benzyl,

C_{1-6} alkyl optionally substituted by R^{21}

or

C_{1-6} alkoxy optionally substituted by R^{21}

wherein

R^{21} represents cyano, mono-, di or tri- halogen, hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (hydroxyC_{1-6} alkyl) amino, N- (halophenylC_{1-6} alkyl) amino, amino C_{2-6} alkylenyl, C_{1-6} alkoxy, hydroxyC_{1-6} alkoxy, -C(O)- R^{201}, -NHC(O)- R^{201}, C_{3-8}cycloalkyl, isoindolino, phthalimidyl, 2-oxo-1,3-oxazolidinyl, aryl or a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N optionally substituted by

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, aminoC_{1-6}alkyl, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino, or benzyl,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N- (halophenylC_{1-6} alkyl) amino, C_{1-6}alkyl, aminoC_{1-6} alkyl, aminoC_{2-6} alkylenyl, C_{1-6} alkoxy, a 5 or 6 membered saturated or unsaturated heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting O, S and N optionally substituted by

hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, hydroxyC_{1-6} alkoxy, oxo, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6} acyl)amino or benzyl;

R^3 represents hydrogen, halogen, aminocarbonyl, or C_{1-6} alkyl optionally substituted by aryl C_{1-6} alkoxy or mono-, di- or tri- halogen;

R^4 represents hydrogen or C_{1-6} alkyl;

R^5 represents hydrogen or C_{1-6} alkyl; and

R^6 represents halogen, hydrogen or C_{1-6} alkyl.

The compounds of the present invention show PI3K inhibitory activity and PI3K-γ inhibitory activity. They are, therefore, suitable for the production of medicament or medical composition, which may be useful for treatment and prophylaxis of PI3K and/or PI3K-γ related diseases for example, inflammatory and immunoregulatory disorders, such as asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis, and Graves' disease, myocardial contractility disorders, heart failure, thromboembolism, ischemia, cardiac hypertrophy, atherosclerosis and cancer such as skin cancer, bladder cancer, breast cancer, uterus cancer, ovary cancer, prostate cancer, lung cancer, colon cancer, pancreas cancer, renal cancer, gastric cancer, brain tumor, leukemia, etc.

The compounds of the present invention are also useful for treatment of pulmonary hypertension, renal failure, Huntington's chorea and cardiac hypertrophy, as well as neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, diabetes and focal ischemia, since the diseases also relate to PI3K activity in a human or animal subject.

This invention is also to provide a method for treating or preventing a disorder or disease associated with PI3K activity, especially with PI3K-γ activity, in a human or animal subject, comprising administering to said subject a therapeutically effective amount of the fused azolepyrimidine derivatives shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof.

Further this invention is to provide a use of the fused azolepyrimidine derivatives shown in the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof in the preparation of a medicament.

In one embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof; wherein

X represents CR^5R^6 or NH;

Y^1 represents CR^3 or N;

Chemical bond between Y^2═Y^3 represents a single bond or double bond,
with the proviso that when the Y^2═Y^3 represents a double bond,
Y^2 and Y^3 independently represent CR^4 or N, and
when Y^2═Y^3 represents a single bond, Y^2 and Y^3 independently represent CR^3R^4 or NR^4;

Z^1, Z^2, Z^3 and Z^4 independently represent CH, CR^2 or N;

R^1 represents
C_{1-6} alkyl optionally substituted by
mono-, di- or tri- halogen, phenyl, methoxyphenyl, phenoxy, or thienyl,
C_{1-6} alkoxy optionally substituted by mono-, di- or tri- halogen, phenyl, methoxyphenyl, phenoxy, or thienyl,

or

one of the following carbocyclic and heterocyclic rings selected from the group consisting of cyclopropyl, cyclohexyl, piperidinyl, piperazinyl, pyrrolyl, pyrazolyl, furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, isoimidazolyl, pyrazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1-benzothiophenyl, benzothiazolyl, benzimidazolyl, 3H-imidazo[4,5-b]pyridinyl, benzotriazolyl, indolyl, indazolyl, imidazo[1,2-a]pyridinyl, quinolinyl, and 1,8- naphthyridinyl,

wherein

said carbocyclic and heterocyclic rings optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6}acyl)amino, N-(C_{1-6}alkoxycarbonyl)amino, N-(formyl)-N-(C_{1-6}alkyl)amino, N[N,N-di(C_{1-6}alkyl)amino methylene]amino, N[N,N-di(C_{1-6}alkyl)amino (C_{1-6}alkylene)methylene]amino, N-[N,N-di(C_{1-6}alkyl)amino C_{2-6}alkenyl]amino, C_{1-6} alkylthio, C_{1-6}alkanesulfonyl, sulfamoyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, pyridyl, phenyl C_{1-6}alkoxycarbonyl,

thiazolyl optionally substituted by

pyridyl,

piperazinyl optionally substituted by C_{1-6} alkyl or C_{1-6}alkoxy

and

C_{1-6}alkyl optionally substituted by mono-, di- or tri- halogen;

R^2 represents hydroxy, halogen, nitro, cyano, carboxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxy C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxy C_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, C_{2-6}alkenyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}acyloxy, aminoC_{1-6} acyloxy, furyl, morpholino, phenyl, piperidino, aryl,

pyrrolidinyl optionally substituted by C_{1-6}acylamino,
piperidino optionally substituted by hydroxy, C_{1-6} alkyl, carboxy, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)aminocarbonyl,

piperazinyl optionally substituted by C_{1-6} alkyl,

C_{1-6} alkyl optionally substituted by cyano, mono-, di- or tri- halogen, hydroxy, amino, N-(C_{1-6}alkyl)amino, N-(hydroxy C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, C_{3-6} cycloalkyl, tetrazolyl, tetrahydropyranyl, morpholino, phthalimidyl, 2-oxo-1,3oxazolidinyl, phenyl,
-C(O)- R^{201},

pyrrolidinyl optionally substituted by C_{1-6}acylamino,
piperidino optionally substituted by hydroxy, C_{1-6} alkyl, carboxy, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)aminocarbonyl,

or
piperazinyl optionally substituted by C_{1-6} alkyl,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(halobenzyl)amino, C_{1-6}alkyl, C_{1-6} alkoxy, tetrazolyl, tetrahydropyranyl, morpholino,
pyrrolidinyl optionally substituted by C_{1-6}acylamino,
piperidino optionally substituted by hydroxy, C_{1-6} alkyl, carboxy, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)aminocarbonyl,
or
piperazinyl optionally substituted by C_{1-6} alkyl,
C_{1-6} alkoxy optionally substituted by cyano, mono-, di- or tri- halogen, hydroxy, C_{1-6}alkoxy, hydroxy C_{1-6} alkoxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alk-

yl)amino, pyrrolyl, tetrazolyl, tetrahydropyranyl, morpholino, phthalimidyl, 2-oxo-1,3oxazolidinyl, phenyl, -C(O)- R^{201},

pyrrolidinyl optionally substituted by C_{1-6}acylamino,

piperidino optionally substituted by hydroxy, C_{1-6} alkyl, carboxy, aminocarbonyl, N-(C_{1-6}-alkyl)aminocarbonyl, or N,N-di(C_{1-6}-alkyl)aminocarbonyl,

or

piperazinyl optionally substituted by C_{1-6} alkyl,

wherein

R^{201} represents hydroxy, amino, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N(halobenzyl)amino, C_{1-6} alkyl, C_{1-6} alkoxy, amino C_{2-6} alkylenyl, tetrazolyl, tetrahydropyranyl, morpholino,

pyrrolidinyl optionally substituted by C_{1-6}acylamino,

piperidino optionally substituted by hydroxy, C_{1-6} alkyl, carboxy, aminocarbonyl, N-(C_{1-6}alkyl)aminocarbonyl, or N,N-di(C_{1-6}alkyl)aminocarbonyl,

or

piperazinyl optionally substituted by C_{1-6}alkyl;

R^3 represents hydrogen, halogen, C_{1-6} alkyl optionally substituted by amino-carbonyl, arylC_{1-6} alkoxy, or mono-, di- or tri-halogen;

R^4 represents hydrogen or C_{1-6} alkyl;

R^5 represents hydrogen or C_{1-6} alkyl; and

R^6 represents hydrogen, halogen or C_{1-6} alkyl.

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof: wherein

X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4;

Chemical bond between Y^2═Y^3 represents a single bond

Z^4 represents CH;

Z^1, Z^2 and Z^3 independently represent N, CH or CR^2;

R^1 represents cyclopropyl, cyclopentyl, cyclohexyl, 2-furyl, 3-furyl, imidazolyl, pyrimidinyl, pyridazinyl, piperazinyl, 1,2,3-thiadiazolyl, 1,3-benzothiazolyl, quinolyl, 3H-imidazo[4,5-b]pyridinyl, 1H-pyrrol-2-yl optionally substituted by C_{1-6}alkyl,

1H-pyrrol-3-yl optionally substituted by C_{1-6}alkyl, pyrazolyl optionally substituted by 1 or 2 C_{1-6}alkyl, isoxazolyl optionally substituted by 1 or 2 C_{1-6}alkyl,

2-thienyl optionally substituted by chloro, nitro, cyano, or C_{1-6} alkyl,

3-thienyl optionally substituted by chloro, nitro, cyano, or C_{1-6} alkyl,

piperidinyl optionally substituted by C_{1-6}alkoxycarbonyl, or benzyloxy-carbonyl,

phenyl optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, N-(C_{1-6}alkyl)amino, N-(C_{1-6}acyl)amino, N-(C_{1-6}alkoxycabonyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(formyl)-N-C_{1-}

$_6$alkyl amino, C_{1-6} alkylthio, C_{1-6}alkanesulfonyl, sulfamoyl, pyrrolyl, imidazolyl, pyrazolyl, and piperazinyl optionally substituted by C_{1-6}alkyl,

pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of chloro, hydroxy, carboxy, C_{1-6}alkoxy, C_{1-6}alkylthio, amino, N-(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(C_{1-6}acyl)amino, N-(C_{1-6}alkane)sulfonyl amino, N[N,N-di(C_{1-6}alkyl)amino methylene]amino, and C_{1-6}alkyl optionally substituted by tri halogen,

pyrazinyl optionally substituted by C_{1-6}alkyl,

1,3-thiazolyl optionally substituted by 1 or 2 substituents selected from the group consisting of C_{1-6}alkyl, pyridyl and N-(C_{1-6}alkoxycrbonyl)amino,
indolyl optionally substituted by C_{1-6}alkyl,
benzimidazolyl optionally substituted by C_{1-6}alkyl or tri-halo C_{1-6}alkyl,
1,2,3-benzotriazolyl optionally substituted by C_{1-6}alkyl, 1,8-naphthyridinyl optionally substituted by
C_{1-6}alkyl optionally substituted by tri halogen,
C_{1-6} alkyl optionally substituted by tri-halogen, phenyl, phenoxy, or thienyl,
or
C_{1-6}alkoxy optionally substituted by phenyl, phenoxy, or thienyl;

R^2 represents fluoro, chloro, bromo, hydroxy, nitro, vinyl, cyano, amino, aminoacetoxy, N-(C_{1-6}alkyl)amino, N,N-di(C_{1-6}alkyl)amino, N-(hydroxyC_{1-6}alkyl)-N-(C_{1-6}alkyl)amino, 2-furyl, piperidino, morpholino, phenyl,

pyrrolidinyl optionally substituted by acetamido,
piperidino optionally substituted by hydroxy,
piperazinyl optionally substituted by methyl, benzyl, C_{1-6}alkoxy-carbonyl, or aminocarbonyl,

C_{1-6} alkyl optionally substituted by cyano, tri-fluoro, carboxy, methoxycarbonyl, aminocarbonyl, tert-butoxycarbonyl, tetrahydropyranyl, or morpholino,

C_{1-6} alkoxy optionally substituted by hydroxy, cyano, methoxy, methoxycarbonyl, tert-butoxycarbonyl, carboxy, aminoacetyl, dimethylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, isopropylaminocarbonyl, fluorobenzylaminocarbonyl, cyclopropyl, pyrrolidinyl, piperidino, tetrahydropyranyl, morpholino, morpholinocarbonyl, 2-oxo-1,3-oxazolidin-4-yl, phthalimid-N-yl, or hydroxy C_{1-6} alkyleneoxy,

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents hydrogen.

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4;

Chemical bond between $Y^2{=}{=}Y^3$ represents a single bond

Z^3 and Z^4 represent CH;

Z^1 and Z^2 independently represent CH or CR^2;

R^1 represents 3H-imidazo[4,5-b]pyridinyl, benzimidazolyl pyridyl optionally substituted by hydroxy, amino, acetamido, methoxybenzyloxy or methyl-sulfonylamino,

or

1,3-thiazolyl optionally substituted by 1 or 2 methyl;

R^2 represents fluoro, chloro, bromo, morpholino, piperazinyl, methyl-piperazinyl, methyl, tri-fluoro methyl, or

C_{1-6} alkoxy optionally substituted by hydroxy, cyano, carboxy, dimethyl-aminocarbonyl, tetrahydropyranyl, morpholino, morpholinocarbonyl, tetrazolyl, or phthalimid-N-yl;

R^3 represents hydrogen;

R^4 represents hydrogen;

R^5 represents hydrogen; and

R^6 represents hydrogen.

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

wherein

X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4;

Chemical bond between $Y^2 \equiv Y^3$ represents a single bond.

Z^3 and Z^4 represent CH;

Z^1 and Z^2 independently represent CH or CR^2;

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4;

Chemical bond between $Y^2 \equiv Y^3$ represents a single bond

Z^1 and Z^4 represent CH;

Z^2 and Z^3 independently represent CH or CR^2;

In another embodiment, the present invention provides the fused azolepyrimidine derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

X represents CR^5R^6 or NH;

Y^1 represents N;

Y^2 and Y^3 represent CR^3R^4;

Chemical bond between Y^2===Y^3 represents a single bond;

Z^1, Z^3 and Z^4 represent CH;

Z^2 represents CR^2;

The preferable compounds of the present invention are as follows:

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-yl-ethylenol;

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

6-(acetamido)-N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-{5-[2-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxy-vinyl]pyridin-2-yl}acetamide;

2-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)-N,N-dimethylacetamide;

2-[7-methoxy-8-(tetrahydro-2H-pyran-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

2-[8-(2-hydroxyethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetic acid;

4-({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)butanoic acid;

({5-[2-hydroxy-2-pyridin-3-ylvinyl]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)acetonitrile;

2-[7-methoxy-8-(2H-tetrazol-5-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

2-[7-methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol;

5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-3-ol ;

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;

6-(acetamido)-N-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;

5-hydroxy-N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-[(4-methoxybenzyl)oxy]nicotinamide;

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-5-hydroxynicotinamide;

5-hydroxy-N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{8-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-(7-bromo-8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

6-amino-N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

1-(1H-benzimidazol-5-yl)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;

2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(2,4-dimethyl-1,3-thiazol-5-yl)ethylenol;

N-(9-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8-bromo-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-(8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-[8-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;

N-(7-fluoro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-(7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

6-(acetamido)-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

1-(1H-benzimidazol-5-yl)-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)ethylenol;

N-{5-[1-hydroxy-2-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)vinyl]pyridin-2-yl}acetamide;

6-methyl-N-(8-morpholin-4-yl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

1-(1H-benzimidazol-5-yl)-2-[8-(4-methylpiperazin-1-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]ethylenol;

N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

N-(7,8-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide;

N-[7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1H-benzimidazole-5-carboxamide;

N-(7,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1H-benzimidazole-5-carboxamide;

N-{5-[2-(7,9-dimethoxy-8-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide;
N-{5-[2-(7-bromo-9-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-hydroxyvinyl]pyridin-2-yl}acetamide; and
2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-pyridin-3-ylethylenol;
and its tautomeric or stereoisomeric form, pharmaceutically acceptable salts thereof.

Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

Alkyl per se and "alk" and "alkyl" in alkane, alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, sec-butyl, pentyl, n-hexyl, and the like.

Alkylene represents the divalent linear or branched saturated hydrocarbon radical, consisting solely of carbon and hydrogen atoms, having generally 1 to 6 carbon preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methylene, ethylene, 2-methyl-propylene, butylene, 2-ethylbutylene and the like.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy, n-hexoxy and the like.

Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-

methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino, N-n-hexyl-N-methylamino and the like.

Alkylaminocarbonyl represents an radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylamino-carbonyl, tert-butyl-aminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, N,N-dimethyl-aminocarbonyl, N,N-diethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-n-propylaminocarbonyl, N-isopropyl-N-n-propylaminocarbonyl, N-t-butyl-N-methylaminocarbonyl, N-ethyl-N-n-pentylamino-carbonyl, N-n-hexyl-N-methylaminocarbonyl and the like.

Alkylaminosulphonyl represents an alkylaminosulphonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminosulphonyl, ethylaminosulphonyl, n-propylaminosulphonyl, isopropyl-aminosulphonyl, tert-butylaminosulphonyl, n-pentylaminosulphonyl, n-hexyl-amino-sulphonyl, N,N-dimethylaminosulphonyl, N,N-diethylaminosulphonyl, N-ethyl-N-methylamino-sulphonyl, N-methyl-N-n-propylaminosulphonyl, N-isopropyl-N-n-propylaminosulphonyl, N-t-butyl-N-methylaminosulphonyl, N-ethyl-N-n-pentyl-aminosulphonyl, N-n-hexyl-N-methylaminosulphonyl and the like.

Alkylsulphonyl illustratively and preferably represents methylsulphonyl, ethyl-sulphonyl, n-propylsulphonyl, isopropylsulphonyl, tert-butyl-sulphonyl, n-pentyl-sulphonyl, n-hexylsulphonyl and the like.

Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxy-carbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxy-carbonyl, n-hexoxycarbonyl and the like.

Alkoxycarbonylamino illustratively and preferably represents methoxycarbonyl-amino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino,

tert-butoxycarbonylamino, n-pentoxycarbonylamino, n-hexoxycarbonylamino and the like.

Alkanoylamino illustratively and preferably represents acetamido, ethylcarbonylamino and the like.

Cycloalkyl per se and in cycloalkylamino and in cycloalkylcarbonyl represents a cycloalkyl group having generally 3 to 8 and preferably 5 to 7 carbon atoms, illustratively and preferably representing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

Aryl per se and "aryl" in arylamino, arylcarbonyl, alkoxyaryl, represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl, phenanthrenyl and the like.

Arylamino represents an arylamino radical having one or two (independently selected) aryl substituents, illustratively and preferably representing phenylamino, diphenylamino, naphthylamino and the like.

Heteroaryl per se and "heteroaryl" in heteroarylamino and heteroarylcarbonyl represents an aromatic mono- or bicyclic radical having generally 5 to 15 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiazolyl, pyrazinyl, pyridinyl, pyrimidinyl, pyridazinyl, thiophenyl, indolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl, 1,3 benzodioxole, benzofuranyl, benzofuran-2,5-diyl, benzofuran-3,5-diyl, and the like.

Heterocyclic per se and heterocyclic ring per se represent a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to

10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholino, perhydroazepinyl.

Heterocyclylcarbonyl illustratively and preferably represents tetrahydrofuran-2-carbonyl, pyrrolidine-2-carbonyl, pyrrolidine-3-carbonyl, pyrrolinecarbonyl, piperidinecarbonyl, morpholinecarbonyl, perhydroazepinecarbonyl.

Halogen and Halo represents fluoro, chloro, bromo and/or iodo.

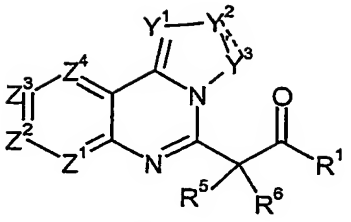
Further, the present invention provides a medicament which include one of the compounds described above and optionally pharmaceutically acceptable excipients.

EMBODIMENT OF INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by reactions described below. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3^{nd} Edition)" by Greene and Wuts.

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A], and [B] below.

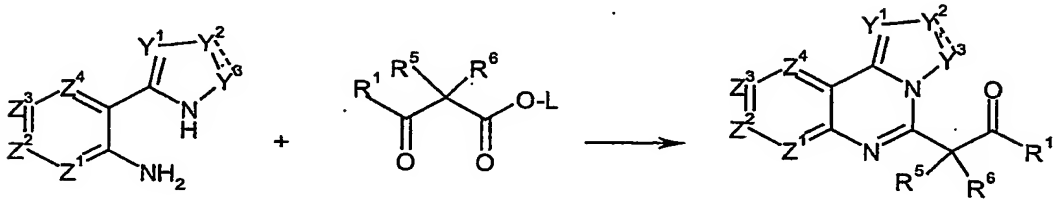
The compound of the formula (I-a):



I-a

(wherein R^1, R^5, R^6, Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be, but not limited to be, prepared by the following Method A.

Method [A]



II III I-a

The compound of formula (I-a) can be prepared, for example, by the reaction of the compound of formula (II) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with a compound of formula (III) (wherein R^1, R^5 and R^6 are the same as defined above, and L represents C_{1-6} alkyl).

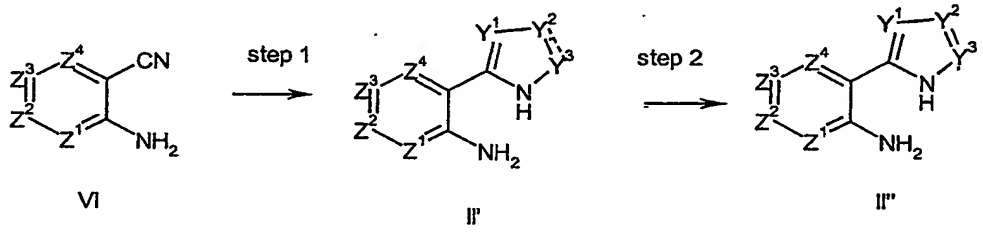
The reaction may be carried out without solvent, or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethyl-acetamide and N-methylpyrrolidone; sulfoxides such as dimethylsulfoxide (DMSO); alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; water, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 10°C to 200°C and preferably about 50°C to 160°C. The reaction may be conducted for, usually, 10 minutes to 48 hours and preferably 30minutes to 24 hours.

Preparation of the intermediates

The compound of formula (II') (wherein Y^1, Z^1, Z^2, Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 and are connected by single bond) and the compound of formula (II") (wherein Y^1, Z^1, Z^2, Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CH or N and are connected by double bond) can be, but not limited to be, prepared by the following Method [A-i].

Method [A-i]



VI II' II"

In the step 1, the compound of formula (II') (wherein Y^1, Z^1, Z^2, Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 and are connected by single bond) can be prepared, for example, by the reaction of the compound of formula (VI) (wherein Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with an diaminoalkane derivatives such as ethylenediamine.

The reaction can be advantageously carried out using appropriate dehydrating agents such as $SOCl_2$, $POCl_3$, P_2O_5, P_2S_5, CS_2 and others.

The reaction may be carried out without solvent, or in a solvent including for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran

(THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 10°C to 200°C and preferably about 50°C to 200°C. The reaction may be conducted for, usually, 10 minutes to 48 hours and preferably 30minutes to 24 hours.

In the step 2, the compound of formula (II'') (wherein Y^1, Z^1, Z^2, Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CH or N and are connected by double bond) can be prepared, for example, from the compound of formula (II') (wherein Y^1, Z^1, Z^2, Z^3 and Z^4 are the same as defined above, Y^2 and Y^3 independently represent CR^3R^4 or NR^4 and are connected by single bond) by the oxidation reaction using an agent such as MnO_2, $KMnO_4$ and others, or by the dehydrogenation reaction using palladium on carbon.

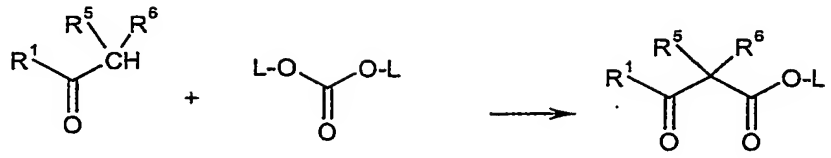
The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dimethylformamide (DMF), dimethylacetamide(DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 50°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

The compound of formula (VI) is commercially available or can be synthesized by conventional method.

The compound of formula (III) can be prepared, for example, by the following Method [A-ii].

Method [A-ii]



VII VIII III

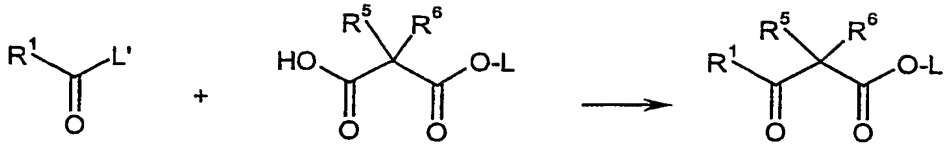
The compound of formula (III) (wherein L, R^1, R^5 and R^6 are the same as defined above) can be prepared by the reaction of the compound of formula (VII) (wherein R^1, R^5 and R^6 are the same as defined above) with the compound of formula (VIII) (wherein L is the same as defined above) in the presence of a base such as potassium hydride, potassium hexamethyldisilazide, and others.

The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, dimethylformamide (DMF), dimethylacetamide(DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about -100°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

Alternatively, the compound of formula (III) can be prepared, for example, by the following Method [A-iii].

Method [A-iii]

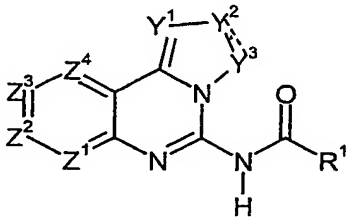


IX X III

The compound of formula (III) (wherein L, R^1, R^5 and R^6 are the same as defined above) can be prepared by the reaction of the compound of formula (IX) (wherein R^1 is the same as defined above and L' is a leaving group such as halogen atom e.g., chlorine or bromine atom, or imidazole) with the compound of formula (X) (wherein wherein L, R^5 and R^6 are the same as defined above) or its salts, for example, potassium salt.

The reaction can be carried out in the presence of Lewis acid including magnesium salts, such as magnesium bromide, magnesium chloride, magnesium iodide, magnesium acetate, and others or a base such as n-butyl lithium, sec-butyl lithium, and others. The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

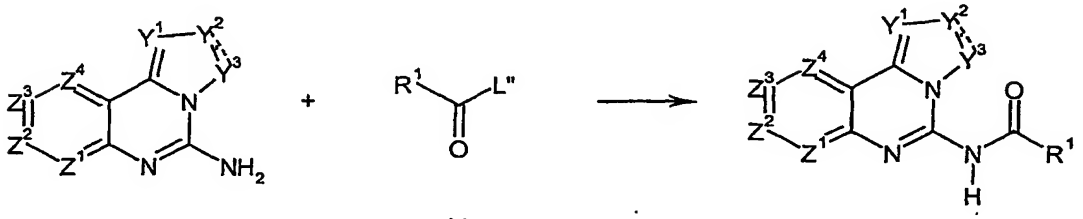
The preparation of the compound formula (I-b):



I-b

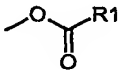
(wherein R^1, Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be, but not limited to be, prepared by the following Method B.

Method [B]

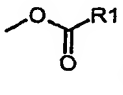


IV V I-b

The compound of formula (I-b) can be prepared, for example, by the reaction of the compound of formula (IV) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with a compound of formula (V) (wherein R^1 is the same as defined above and L" is a leaving group, such as hydroxy; halogen atom e.g., chlorine, bromine, or iodine



atom; imidazole or, wherein R^1 is the same as defined above). In the case L" is hydroxy, the reaction can be advantageously carried out by using a coupling agent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 1,1'-carbonyldi(1,3-imiazole)(CDI), 1,1'-carbonyldi(1,2,4-triazole)(CDT) and others.

In the case L" is halogen atom, imidazole, or  the reaction can be advantageously conducted in the presence of a base, including, for instance, such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, and others.

The reaction may be carried out without solovent, or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide

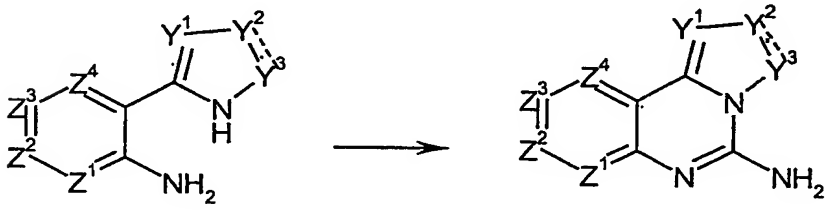
(DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 40°C to 200°C and preferably about 20°C to 180°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

Preparation of intermediates

The compound of formula (IV) can be, but not limited to be, prepared by the following Method [B-i]:

Method [B-i]



II IV

The compound of formula (IV) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be prepared by the reaction of compound of formula (II) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) with cyanogen halides such as cyanogen bromide.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-

methylpyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about -10°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 hour to 24 hours.

The compound of formula (II) (wherein Y^1, Y^2, Y^3, Z^1, Z^2, Z^3 and Z^4 are the same as defined above) can be obtained in the same manner described in Method [A-i].

The compound of formula (VII), (VIII), (IX) and (X) are commercially available or can be synthesized by conventional method.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon(s) in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by the reaction of the compound of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal

hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tri(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring

agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and a sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg/kg/day to about 100mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In case of parenteral administration, it has generally proven

advantageous to administer quantities of about 0.001 to 100 mg/kg/day, preferably from 0.01 mg/kg/day to 1mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Examples

The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H). Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mm ϕ X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate. Mass spectra were obtained using electrospray (ES) ionization techniques (Micromass Platform LC). TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Kanto Chemical Co., Ltd.

The effects of the compounds of the present invention were examined by the following assays.

[Determination of IC50 values of compounds in kinase assay of PI3Kγ]

Chemicals and assay materials

Phosphatidylinositol (PtdIns) and phosphatidylserine (PtdSer) were purchased from DOOSAN SERDARY RESEARCH LABORATORIES (Toronto, Canada). Recombinant human PI3Kγ (full length human PI3K p110γ fused with a His_6-tag at the C-terminus expressed in *S. frugiperda* 9 insect cells) was obtained from ALEXIS BIOCHEMICALS (#201-055-C010; San Diego, CA). [γ^{33}P]ATP and unlabeled ATP were purchased from AMERSHAM PHARMACIA BIOTECH (Buckinghamshire, UK) and ROCHE DIAGNOSTICS (Mannheim, Germany), respectively. Scintillation cocktails and MicroScint PS™ were purchased from PACKARD (Meriden, CT). Maxisorp™ plates were purchased from NALGE NUNC INTERNATIONAL K.K. (Tokyo, Japan). All other chemicals not further specified were from WAKO PURE CHEMICALS (Osaka, Japan).

Solid-Phase Lipid Kinase Assay

To assess inhibition of PI3Kγ by compounds, the Maxisorp™ plates were coated with 50 µl/well of a solution containing 50 µg/ml PtdIns and 50 µg/ml PtdSer dissolved in chloroform:ethanol (3:7). The plates were subsequently air-dried by incubation for at least 2 hours in a fume hood. The reaction was set up by mixing 25 µl/well of assay buffer 2x (100 mM MOPSO/NaOH, 0.2 M NaCl, pH 7.0, 8 mM $MgCl_2$, 2 mg/ml BSA (fatty acid-free)) and 50 ng/well PI3Kγ in the lipid pre-coated plate and 10x test compounds were added in 2% DMSO. The reaction was started by adding 20 µl/well of ATP mix (final 10 µM ATP; 0.05 µCi/well [γ^{33}P]ATP). After incubation at RT for 2 hours, the reaction was terminated by adding 50 µl/well stop solution (50 mM EDTA, pH 8.0). The plate was then washed twice with Tris–buffered saline (TBS, pH 7.4). MicroScint PS™ (PACKARD) scintillation mix was added at 100 µl/well, and radioactivity was counted by using a TopCount™ (PACKARD) scintillation counter.

The inhibition percent at each concentration of compound was calculated, and IC50 values were determined from the inhibition of curve.

[Isozyme selectivity test in PI3K]

{Determination of IC50 values of compounds in kinase assay of PI3Kβ}

Recombinant baculovirus of PI3Kβ p110β and GST-p85α were obtained from Dr. Katada (University of Tokyo). Recombinant PI3K heterocomplex of p110β and GST-p85α were co-expressed in insect cells according to manufacture's instruction (Pharmingen, San Diego, CA), and purified with glutathione affinity column. Kinase assay of PI3Kβ was prepared in a similar manner as described in the part of [Determination of IC50 values of compounds in kinase assay of PI3Kγ].

[Selectivity test with other kinases]

Kinase selectivity of the compounds was assessed by using a few kinase assaies such as kinase assay of Syk.

{Syk tyrosine kinase inhibitory assay for selectivity}

(1) Preparation of Syk protein

A cDNA fragment encoding human Syk openreading frame was cloned from total RNA of human Burkitt's lymphoma B cell lines, Raji (American Type Culture Collection), with the use of RT-PCR method. The cDNA fragment was inserted into pAcG2T (Pharmingen, San Diego, CA) to construct a baculovirus transfer vector. Then the vector, together with the linearized baculovirus (BaculoGoldTM, Pharmingen), was used to transfect Sf21 cells (Invitrogen, San Diego, CA).

Generated recombinant baculovirus was cloned and amplified in Sf21 cells. Sf21 cells were infected with this amplified high titer virus to produce a chimeric protein of Syk kinase fused by glutathione-S-transferase (GST).

The resulting GST-Syk was purified with the use of glutathione column (Amersham Pharmacia Biotech AB, Uppsala, Sweden) according to the manufacturer's instruction. The purity of the protein was confirmed to be more than 90% by SDS-PAGE.

(2) Synthesize of a peptide

Next, a peptide fragment of 30 residues including two tyrosine residues, KISDFGLSKALRADENYYKAQTHGKWPVKW, was synthesized by a peptide synthesizer. The N-terminal of the fragment was then biotinylated to obtain biotinylated activation loop peptide (AL).

(3) The measurement of Syk tyrosine kinase activity

All reagents were diluted with the Syk kinase assay buffer (50 mM Tris-HCl (pH 8.0), 10 mM $MgCl_2$, 0.1 mM Na_3VO_4, 0.1% BSA, 1 mM DTT). First, a mixture (35 µl) including 3.2 µg of GST-Syk and 0.5 µg of AL was put in each well in 96-well plates. Then 5µl of a test compound in the presence of 2.5% dimethyl sulfoxide (DMSO) was added to each well. To this mixture was added 300 µM ATP (10 µl) to initiate the kinase reaction. The final reaction mixture (50 µl) consists of 0.65 nM GST-Syk, 3 µM AL, 30 µM ATP, a test compound, 0.25% DMSO, and a Syk kinase assay buffer.

The mixture was incubated for 1 hour at room temperature (RT), and the reaction was terminated by the addition of 120 µl of termination buffer (50 mM Tris-HCl (pH 8.0), 10 mM EDTA, 500 mM NaCl, 0.1% BSA). The mixture was transferred to streptavidin-coated plates and incubated for 30 minutes. at room temperature to

combine biotin-AL to the plates. After washing the plates with Tris-buffered saline (TBS) (50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl) containing 0.05% Tween-20 for 3 times, 100 µl of antibody solution consisting of 50 mM Tris-HCl (pH 8.0), 138 mM NaCl, 2.7 mM KCl, 1% BSA, 60 ng/ml anti-phosphotyrosine monoclonal antibody, 4G10 (Upstate Biotechnology), which was labeled with europium by Amersham Pharmacia's kit in advance, was added and incubated at room temperature for 60 minutes. After washing, 100 µl of enhancement solution (Amersham Pharmacia Biotech) was added and then time-resolved fluorescence was measured by multi-label counter ARVO (Wallac Oy, Finland) at 340 nm for excitation and 615 nm for emission with 400 msec of delay and 400 msec of window.

[Determination of IC50 values of compounds in superoxide generation from human peripheral mononuclear cells]

Blood (100 ml/donor) was taken from healthy human volunteers by venepuncture with 50 ml syringes containing 50 units heparin. Red blood cells were removed by incubation with 1% (w/v) dextran and 0.45% (w/v) glucose for 30 minutes at room temperature. After centrifugation at 350 xg for 10 minutes, the cell pellet was resuspended in 10 ml PBS. The cell suspension was gently layered on 20 ml of 60% and 20ml of 80% Percoll (Amersham Pharmacia Biotech, Sweden) gradient in PBS in 50 ml tube (#2335-050, Iwaki, Japan). After centrifugation at 400 xg for 30 minutes at room temperature, peripheral polymorphonuclear leukocytes (PMNs) were obtained from the interference between 60% and 80% Percoll phases. After twice washing in PBS, PMNs were suspended at a density of 10^7 cells/ml in Hank's Balanced Salt Solution (HBSS: Nissui, Japan) supplemented by 10 mM Na-Hepes (pH 7.6), 0.1% BSA and kept on ice until further use.

To test inhibition of formyl-methionyl-leucyl-phenylalanine (fMLP)-induced superoxide generation by compounds, PMNs (2 x 10^5 cells/well) were seeded in HBSS, 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well clear bottom black plate (Cat.#3904, Costar) and pretreated with luminol (1 µg/well; Sigma) and test

compounds for 10 minutes at 37°C. fMLP peptide (Cat.#4066; Peptide Institute Inc, Japan) was prepared in 10 μM in the same buffer and prepared in a polypropylene plate (Cat.#3365, Coster). Chemiluminescence (CL) was measured by FDSS-6000 (Hamamatsu Photonics) over 15 minutes after stimulation with 1 μM fMLP. The percentage of inhibition at each concentration of compound was calculated based on the first peak of CL at approximately 1 minute after addition of stimulus and IC50 values were determined from the inhibition curve.

For opsonized zymosan (OZ) and phorbol 12-myristate 13-acetate (PMA) stimulation, Zymosan A (Sigma) was suspended in HBSS at a concentration of 1 mg/ml and incubated with human pooled serum at a final concentration range of 9 to 80% at 37°C for 30 minutes to opsonize the zymosan, followed by centrifugation at 500×g for 10 minutes at 4°C. Then the sediments were washed twice in HBSS and finally resuspended in HBSS to a concentration between 1 and 10 mg/ml. Opsonized zymosan (OZ) was used at 5 mg/ml for stimulation. Phorbol12-myristate 13-acetate (PMA) was initially dissolved at a concentration of 0.1 mg/ml in DMSO as a stock solution and stored frozen at -20°C. PMA solution was prepared from the stock solution by further dilution in HBSS to the concentration of 100 ng/ml. PMNs (2 x 10^5 cells/well) were seeded in HBSS, 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well white plate (Packard) and pretreated with luminol (1 μg/well; Sigma) and test compounds for 10 minutes at 37°C. CL was measured by Arvo counter (Wallac)) at 30 minutes after the stimulation with OZ or PMA. The percentage of inhibition at each concentration of compound was calculated and IC50 values were determined from the inhibition curve.

[Determination of IC50 values of compounds in elastase release from human peripheral mononuclear cells]

To test inhibition of elastase release by compounds, PMNs (5 x 10^5 cells/well) were seeded in HBSS supplemented with 10 mM Na-Hepes (pH 7.6), 0.1% BSA in 96-well plate. Cells were pretreated with cytochalasine B (0.1 μg/well; Nakarai, Japan)

and test compounds in 90 µl/well for 10 minutes at 37°C. Cells were stimulated with 1 µM fMLP for 15 minutes at 37°C. Supernatants (40 µl/well) were collected into 384 well black plate (Packard) to measure elastase activity. Fluorescent-based elastase reaction was started by the addition of 10 µl of 0.5 mM Suc-Ala-Ala-Ala-MCA (Cat. #3133v; Peptide Institute Inc, Japan) into the 384 well plate at room temperature. The fluorescence emission was measured at 460 nm (λex, 360 nm) by using a Wallac-Arvo counter (PerkinElmer, Boston, MA) fluorescence plate leader for 120 minutes. IC50 values of compounds were determined at the initial velocity of the reaction.

[Determination of IC50 values of compounds in chemotaxis assay with the use of human PMNs]

Freshly prepared PMNs (1.1 x 10^7 cells/ml) were incubated with compounds in a polypropylene 96 well plate (Cat.#3365, Coster) for 10 minutes in HBSS supplemented with 10 mM Na-Hepes (pH 7.6), 0.1% BSA. Cells (100 µl) were incubated with test compounds or vehicle for 30 minutes and were transferred into an Multiwell insert (Cat.# 351183; Falcon) 24w plate. FMLP (10 nM, 0.5 ml) was added into the lower chamber of the plate, and chemotaxis was measured in CO_2 incubator at 37°C for 1 hour. Migrated cells were counted using FACScan (Becton Dickinson, Franklin Lakes, NJ). The percentage of inhibition at the each concentration of compound was calculated, and the IC50 values were determined from the inhibition curve.

[Determination of IC50 values of compounds in chemotaxis assay with the use of transfectants]

(1) cell

Human CCR3-transformed L1.2 cells were used. Human CCR3-expressing L1.2 stable transformant was established by electroporation, referring to the methods described in J. Exp. Med. 183:2437-2448, 1996. The human CCR3-transformed L1.2

cells were maintained in RPMI-1640 supplemented with 10% FCS , 100 units/ml of penicillin G and 100 μg/ml of streptomycin, and 0.4 mg/ml of Geneticin. One day before the chemotaxis assay, cells were pretreated with 5 mM sodium butyrate - containing culture medium (5 x 10^5cells/ml) for 20-24 hours to increase the expression of CCR3.

(2) Chemotaxis assay

Butyrate-pretreated cells were suspended in chemotaxis buffer (Hanks' solution Cat.#05906 Nissui, 20 mM HEPES pH 7.6, 0.1% human serum albumin Cat.#A-1887 Sigma) at a cell density of 1.1 x 10^7 cells /ml. A mixture of 90 μl of cell suspension and 10 μl of compound solution diluted with chemotaxis buffer (10-times concentration of the final concentration) were preincubated for 10 minutes at 37°C. The mixture of cells and compounds was added into the upper chamber of the 24-well chemotaxis chamber (Transwell™, Cat.#3421, Costar, pore size;5 μm). 0.5 ml of 10 nM of human recombinant eotaxin (Cat.#23209, Genzyme Techne) solution, diluted with chemotaxis buffer, was added into the lower chamber of the chemotaxis plate. Then, chemotaxis was performed in CO_2 incubator at 37°C for 4 hours. After 4hours incubation, migrated cells were counted using FACScan (Becton Dickinson). The percentage of inhibition at the each concentration of compound was calculated, and IC50 values were determined from the inhibition curve.

[Mouse fMLP-induced pleurisy Model]

Seven weeks old BALB/c female mice were divided into 3 groups, a nontreatment group, a vehicle group and a treatment group. Mice in the treated group were first injected intravenously with compounds of the present invention at varied doses. Mice in the vehicle group were injected with vehicle containing 10% Cremophor EL (Nacalai Tesque) in saline. Three minutes after the treatment, a solution containing 1 mg/mouse of fMLP in 3.3% DMSO in PBS was administrated intrapleuraly into a vehicle group and a treated group mice. Four hours after fMLP-injection, mice were

sacrificed and pleural fluid was collected by washing the pleural cavity twice with 2 ml PBS. Total cells per milliliter of pleural fluid were counted using a hemacytometer. Cell differentiation of pleural fluid was determined by counting a minimum of 200 cells from a Giemsa's-stained cytospin slide preparation. Statistical analysis was performed by means of Student's t-test for paired data or analysis of variance with Dunnett's Post test , using GraphPadPRISM for Windows, version 2.01.

For practical reasons, the compounds are grouped in some classes of activity as follows:

In vitro IC_{50} = A (= or <) 0.1 μM < B (= or <) 0.5 μM < C (= or <) 2 μM < D

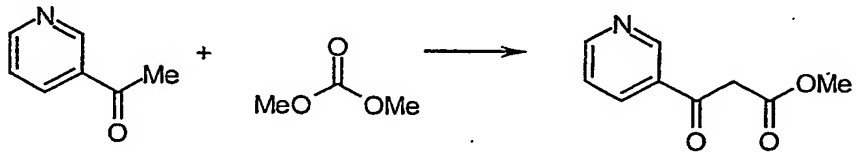
The compounds of the present invention also show strong activity in vivo assays.

(dec.) in the following tables represents decomposition.

Example 1-1:

Z)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)-1-(3-pyridinyl)ethenol

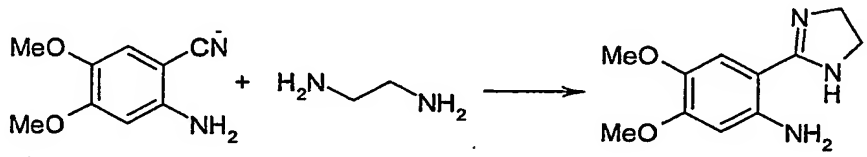
(1) Methyl 3-oxo-3-(3-pyridinyl)propanoate



A 0.5 M solution of pottasium hexamethyldisilazide in toluene (22 ml, 11 mmol) was mixed with tetrahydrofuran (5 ml), and the mixture was cooled at -78°C. To the cold (-78°C) mixture was added dropwise a solution of 3-acethylpyridine (1.0 g, 8.26 mmol) in tetrahydrofuran (5 ml). The mixture was warmed to room temperature

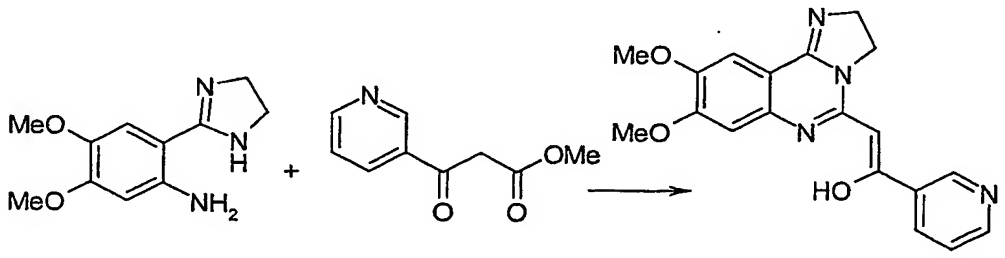
and stirred for 3 hours. The mixture was cold at -78°C, and then dimethyl carbonate (1.2 ml, 14.3 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction solution was quenched by adding aqueous 1N HCl solution, and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (hexane/ ethyl acetate, 1/1) to give methyl 3-oxo-3-(3-pyridinyl)propanoate (1.0 g, 68% yield) as an oil.

(2) 2-(4,5-Dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline:



2-Amino-4,5-dimethoxybenzonitrile (5.0 g, 28 mmol) was added to ethylenediamine (7.9 g, 131 mmol) at room temperature. The resulting solution was warmed to 40., and a catalitic amount of diphosphorus pentasulfide (50 mg) was added. The mixture was heated to 80-90 ., and the stirring was continued overnight. The reaction mixture was diluted with water, and the resulting precipitae was collected by filtration to give 2-(4,5-dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline (5.1 g, 82 %) as a solid.

(3) (*Z*)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)-1-(3-pyridinyl)ethenol



A mixture of 2-(4,5-dihydro-1H-imidazol-2-yl)-4,5-dimethoxyaniline (0.15 g, 0.68 mmol) and methyl-3-oxo-3(3-pyridinyl)propanoate (0.20 g, 1.12 mmol) was stirred at 155. for 1 hour. The reaction mixture was purified by column chromatography on silica-gel (dichloromethane/ methanol, 25/1) to give (Z)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl) ethenol (66.9mg, 28%) as a yellow solid.

Melting point: 275°C

Mass spectrometry: 351

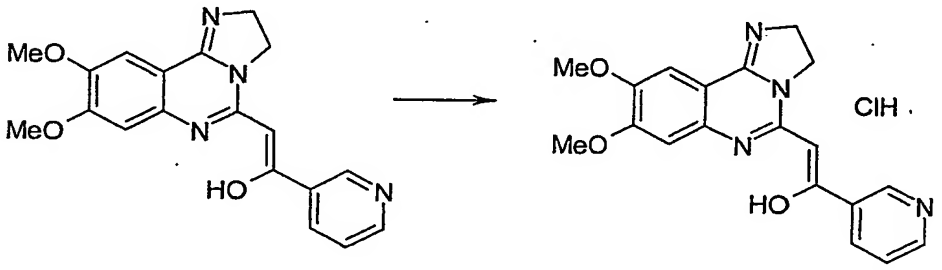
In vitro PI3K-β inhibitory activity: C

In vitro PI3K-γ inhibitory activity: A

^{1}H-NMR (500 MHz, DMSO-d6): d 3.79 (3H, s), 3.88 (3H, s), 3.98-4.08 (4H, m), 5.63 (1H, s), 7.13 (1H, s), 7.24 (1H, s), 7.50 (1H, dd, J = 4.7, 7.8 Hz), 8.27 (1H, dt, J = 1.6, 7.8 Hz), 8.67 (1H, dd, J = 1.6, 4.7 Hz), 9.13 (1H, d, J = 1.6 Hz), 13.9 (1H, bs).

Example 1-2:

(*Z*)-2-(8,9-Dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)-ethenol hydrochloride



To a solution of (*Z*)-2-(8,9-dimethoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol (16.8 mg, 0.05 mmol)) in dioxane (15 ml) at room temperature was added aqueous 6N HCl solution (0.05 ml). After being stirred for 30 minutes, the mixture was dried under reduced pressure to give (Z)-2-(8,9-dimethoxy-2,3-di-

hydroimidazo[1,2-c]quinazolin-5-yl)-1-(3-pyridinyl)ethenol hydrochloride (18.5 mg, quantitative) as a yellow solid.

Melting point: >300°C

Mass spectrometry: 351

In vitro PI3K-β inhibitory activity: C

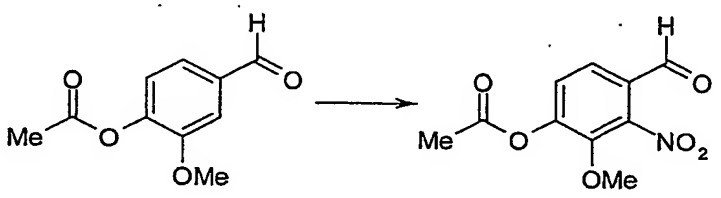
In vitro PI3K-γ inhibitory activity: A

^{1}H-NMR (500 MHz, DMSO-d6): δ 3.88 (3H, s), 4.00 (3H, s), 4.22 (2H, t, J = 9.1 Hz), 4.55 (2H, t, J = 9.1 Hz), 6.21 (1H, s), 7.60 (1H, s), 7.66 (1H, dd, J = 4.7, 8.2 Hz), 7.90 (1H, s), 8.47 (1H, d, J = 8.2 Hz), 8.79 (1H, d, J = 4.7 Hz), 9.28 (1H, s), 14.9 (1H, bs).

Example 1-3:

2-[7-Methoxy-8-(methoxymethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol

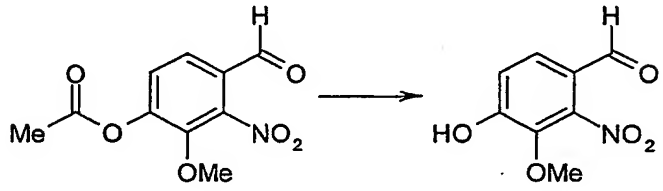
(1) 4-Formyl-2-methoxy-3-nitrophenyl acetate



By the procedure described in US Patent 4287341 or J. Chem. Soc. 376 (1948), vanillin acetate 5.00g afforded the title compound 4.54g as yellow solid. Yield 73.6%.

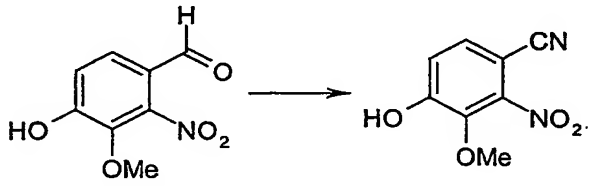
H-NMR (500MHz, DMSO-d_6) δ: 2.40(s 3H), 3.87(s 3H), 7.75(d 1H J=8.4Hz), 7.94(d 1H J=8.4Hz), 9.90(s 1H)

(2) 4-Hydroxy-3-methoxy-2-nitrobenzaldehyde



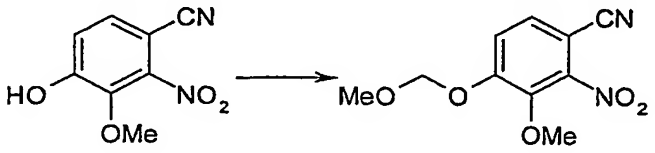
A mixture of 4-formyl-2-methoxy-3-nitrophenyl acetate 4.54g (19.0mmol) and potassium carbonate 5.24g (37.9mmol) in methanol 40mL was stirred at room temperature for 2 hours. The reaction mixture was poured into water, acidified by 1N HCl solution and extracted into AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, filtrated and the solvent was evaporated. The residue was washed with n-hexane to give the title compound 3.60g as white solid. Yield 96.3%.

(3) 4-Hydroxy-3-methoxy-2-nitrobenzonitrile



To a mixture of 4-hydroxy-3-methoxy-2-nitrobenzaldehyde 14.5g (73.5mmol) in 28% ammonia solution 150mL and tetrahydrofuran 15mL was added iodine 22.4g (88.2mmol) and stirred at room temperature for overnight. The reaction mixture was concentrated in vacuo. The residue was acidified with 2H HCl solution and extracted into diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtrated and the solvent was evaporated. The residue was washed with diisopropyl ether to give the title compound 12.1g as brown solid. Yield 84.5%

(4) 3-Methoxy-4-(methoxymethoxy)-2-nitrobenzonitrile



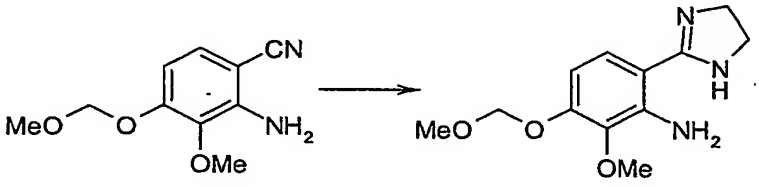
A mixture of 4-hydroxy-3-methoxy-2-nitrobenzonitrile 1.00g, chloromethyl methyl ether 0.47mL (6.18mmol) and potassium carbonate 3.56g (25.8mmol) in N,N-

dimethylformamide 10mL was stirred at 50°C for 2 hours. The reaction mixture was poured into water and extracted into diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$, filtrated and the solvent was evaporated. Silica gel chromatography (n-hexane / AcOEt = 4/1) afforded the title compound 1.03g as colorless solid. Yield 83.5%.

(5) 2-Amino-3-methoxy-4-(methoxymethoxy)benzonitrile

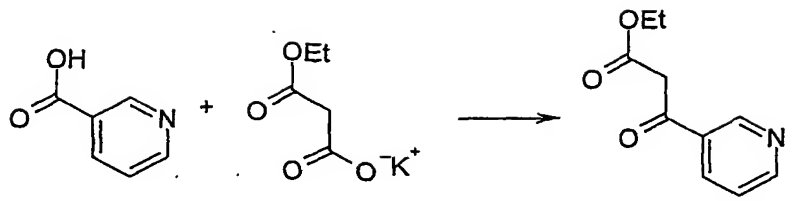
To 5% palladium on activated carbon 6.00g under argon atmosphere was added a solution of 3-methoxy-4-(methoxymethoxy)-2-nitrobenzonitrile 6.00g (25.2mmol) in ethanol 50mL and stirred under hydrogen atmosphere at room temperature for 8 hours. The reaction mixture was filtrated and the filtrate was concentrated in vacuo. Silica gel chromatography (n-hexane / AcOEt = 4/1) afforded the title compound 2.83g as white solid. Yield 53.9%.

(6) [6-(4,5-Dihydro-1H-imidazol-2-yl)-2-methoxy-3-(methoxymethoxy)phenyl]amine



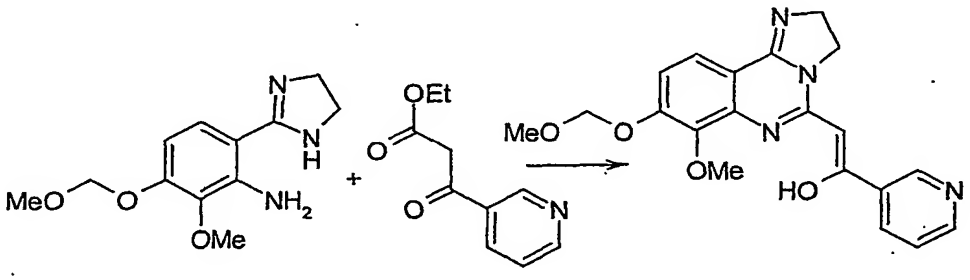
A solution of 2-amino-3-methoxy-4-(methoxymethoxy)benzonitrile 475mg (2.28mmol) and phosphorus pentasulfide 25.4mg (0.11mmol) in ethylenediamine 2.75g was stirred at 120°C for overnight. The reaction mixture was cooled to room temperature and poured into water. The precipitate was collected and washed with water to give the title compound 293mg as white solid. Yield 51.1%.

(7) Ethyl 3-oxo-3-(pyridin-3-yl)propanoate



To a suspension of nicotinic acid 5.00g (40.6mmol) in tetrahydrofuran 50mL was added carbonyl diimidazole 9.76g (60.9mmol) at 5°C and stirred at room temperature for 1 hour. In a separate flask, a suspension of $MgCl_2$ 4.64g (48.7mmol) and ethyl malonate potassium salt 10.37g (60.92mmol) in tetrahydrofuran 50mL was stirred at 50°C for 4 hours. To this suspension was added the aforementioned imidazolide solution at room temperature and stirred for 12 hours. The reaction was quenched by the addition of water and extracted into ethyl acetate. The organic layer was washed by brine, dried over $MgSO_4$, filtrated and the solvent was evaporated. Silica gel chromatography (n-hexane / AcOEt = 2/1) afforded the titla compound 3.89g as pale yellow oil. Yield 49.5%.

(8) 2-[7-Methoxy-8-(methoxymethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol



A solution of [6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxy-3-(methoxymethoxy)phenyl]amine 1.31g (5.20mmol) and ethyl 3-oxo-3-(pyridin-3-yl)propanoate 1.00g (5.20mmol) in toluene 30mL was refluxed for overnight. The precipitate was collected and washed with diethyl ether to give the title compound 1.52g as a yellow solid. Yield 76.9%.

Melting point: 215-216°C

Mass spectrometry: 381

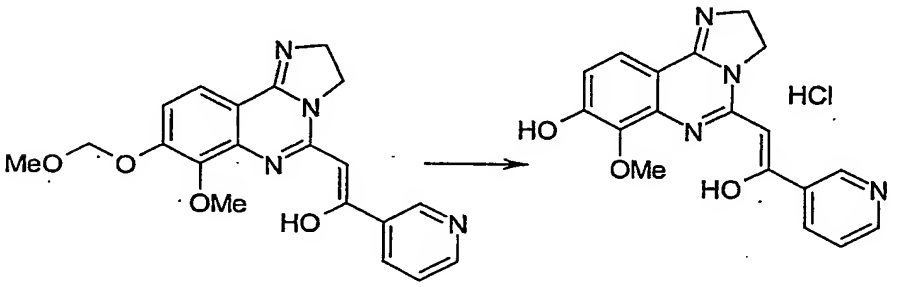
In vitro PI3K-β inhibitory activity:

In vitro PI3K-γ inhibitory activity: B

H-NMR (500MHz, $CDCl_3$) δ: 3.54(s 3H), 3.95(t 2H J=9.5Hz), 4.08(s 3H), 4.22(t 2H J=9.5Hz), 5.30(s 2H), 5.38(s 1H), 6.98(d 1H J=8.8Hz), 7.37(dd 1H J=8.0Hz, 4.9Hz), 7.64(d 1H J=8.8Hz), 8.21(dt 1H J=8.0Hz, 1.7Hz), 8.67(dd 1H J=4.9Hz, 1.7Hz), 9.09(d 1H J=1.7Hz), 13.75(s 1H)

Example 1-4:

5-(2-Hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol hydrochloride



A suspension of 2-[7-methoxy-8-(methoxymethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol (Example 1-3) 1.52g (4.00mmol) in 4N HCl in 1,4-dioxane 30mL and water 0.3mL was stirred at room temperature for overnight. The reaction mixture was diluted with diethyl ether. The precipitate was collected and washed with diethyl ether to give the title compound 1.23g as a yellow solid. Yield 82.4%

Melting point: 245°C

Mass spectrometry: 337

In vitro PI3K-β inhibitory activity: C

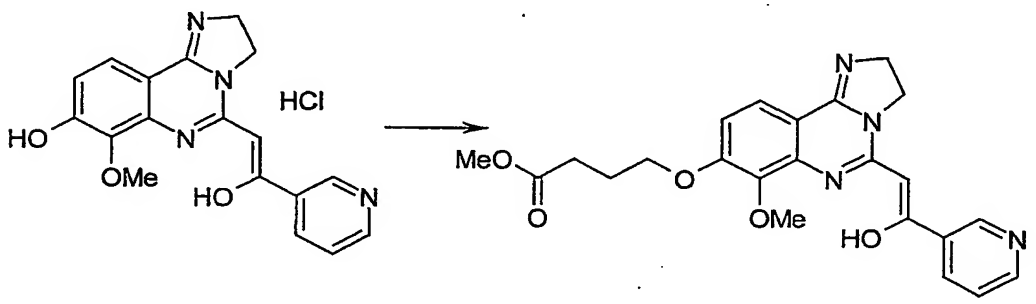
In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, DMSO-d_6) δ: 3.97(s 3H), 4.22(dd 2H J=12.3Hz, 9.0Hz), 4.43(dd 2H J=12.3Hz, J=9.0Hz), 6.17(s 1H), 7.10(d 1H J=9.0Hz), 7.71(dd 1H

J=7.7Hz, 4.7Hz), 7.98(d 1H J=9.0Hz), 8.57(br d 1H J=7.7Hz), 8.82 (dd 1H J=4.7Hz, 1.4Hz), 9.34(d 1H J=1.4Hz), 11.79(s 1H), 14.60(s 1H)

Example 1-5:

Methyl 4-{[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoate



A mixture of 5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol hydrochloride (Example 1-4) 50.4mg (0.14mmol), methyl chlorobutyrate 22.2mg (0.16mmmol) and potassium carbonate 186.9mg (1.35mmmol) in N,N-dimethylformamide 1mL was stirred at 120°C for 4 hours. The reaction mixture was poured into water and extracted into dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtrated and the solvent was evaporated. The residue was washed by diethyl ether to give the title compound 35.0mg as yellow solid. Yield 59.3%.

Melting point: 199-200°C

Mass spectrometry: 437

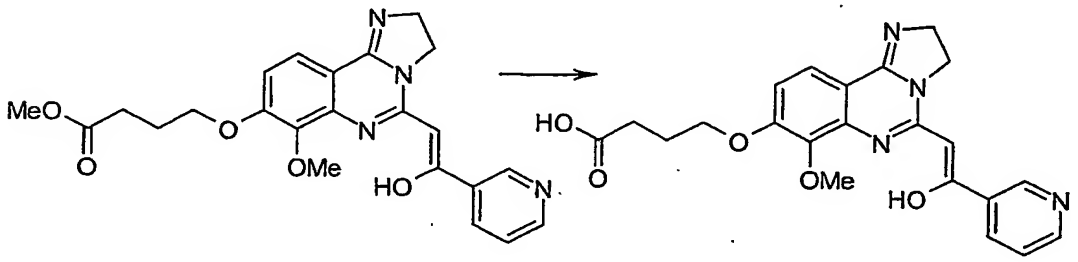
In vitro PI3K-β inhibitory activity: C

In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, $CDCl_3$) δ: 2.20(quint 2H J=7.1Hz), 2.58(t 2H J=7.09Hz), 3.71(s 3H), 3.94(t 2H J=9.5Hz), 4.06(s 3H), 4.15(t 2H J=7.1Hz), 4.21(t 2H J=9.5Hz), 5.38(s 1H), 6.76(d 1H J=8.8Hz), 7.37(dd 1H J=8.2Hz, 5.2Hz), 7.65(d 1H J=8.8Hz), 8.21(dt J=8.2Hz, 2.1Hz), 8.67(d 1H J=5.2Hz), 9.09(s 1H), 13.70(s 1H)

Example 1-6:

Example 3-4; 4-{[5-(2-Hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid



A solution of methyl 4-{[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoate (example 1-5) 20.0mg (0.05mmol) in 1N LiOH solution 0.1mL and ethanol 1.0mL was stirred at room temperature for overnight. The reaction mixture was neutralized with 1N HCl solution and concentrated in vacuo. The residue was triturated in water. The precipitate was collected to give the title compound 10.0mg as white solid. Yield 51.7%.

Melting point: 257-258°C

Mass spectrometry: 423

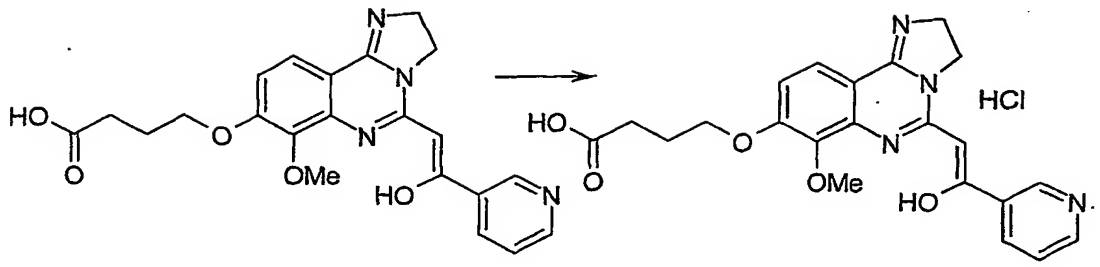
In vitro PI3K-β inhibitory activity: B

In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, DMSO-d_6) δ: 2.02(quint 2H J=6.2Hz), 2.45(t 2H J=6.2Hz), 3.94(s 3H), 3.98(br t 2H J=8.5Hz), 4.06(br t 2H J=8.5Hz), 4.14(t 2H J=6.2Hz), 5.67(s 1H), 6.97(d 1H J=8.7Hz), 7.49(dd 1H J=8.2Hz, 4.4Hz), 7.57(d 1H J=8.7Hz), 8.29(d 1H J=8.2Hz), 8.67(d 1H J=4.4Hz), 9.14(s 1H), 12.15(s 1H), 13.76(s 1H)

Example 1-7:

4-{[5-(2-Hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid hydrochloride



A mixture of 4-{[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid (Example 1-6) 4.0mg (9.5micromol) in 4N HCl in 1,4-dioxane 2.0mL was stirred at room temperature for 2 hours. The reaction mixture was diluted with diethyl ether. The precipitate was collected to give the title compound 4.00mg as a yellow solid. Yield 92.0%.

Melting point: 249-251°C

Mass spectrometry: 423

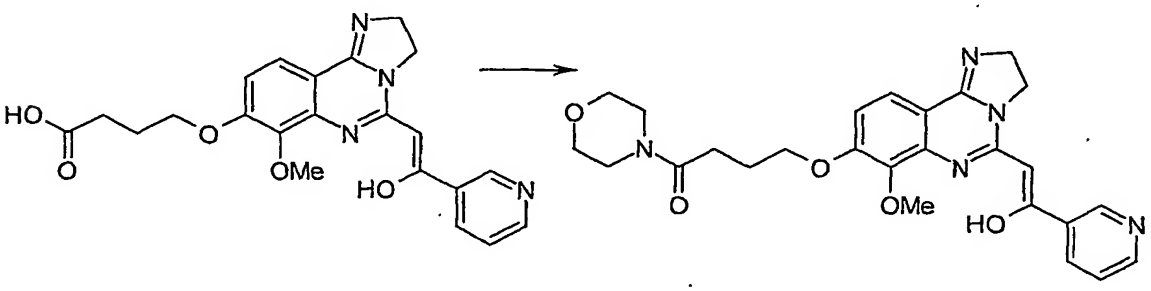
In vitro PI3K-β inhibitory activity: B

In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, DMSO-d_6) δ: 2.06(quint 2H J=7.3Hz), 2.46(t 2H J=7.3Hz), 4.01(s 3H), 4.24(t 2H J=9.0Hz), 4.29(t 2H J=7.3Hz), 4.45(t 2H J=9.0Hz), 6.18(s 1H), 7.36(d 1H J=9.1Hz), 7.70(dd 1H J=7.9Hz, 5.0Hz), 8.14(d 1H J=9.1Hz), 8.56(br d 1H J=7.9Hz), 8.82(br d 1H J=5.0Hz), 9.34(s 1H), 12.34(s 1H), 14.57(s 1H)

Example 1-8:

2-[7-Methoxy-8-(4-morpholin-4-yl-4-oxobutoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-pyridin-3-ylethylenol



To a solution of 4-{[5-(2-hydroxy-2-pyridin-3-ylvinyl)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl]oxy}butanoic acid (Example 1-6) 20.0mg (0.044mmol), morpholine 19.0mg (0.22mmol) and N,N-diisopropylethylamine 0.038mL (0.22mmol) in N,N-dimethylformamide 2.0mL was added PyBOP((1H-1,2,3-benzotriazol-1-yloxy)(tripyrrolidin-1-yl)phosphonium hexafluorophosphate) 34.0mg (0.065mmol) and stirred at 80°C for overnight. After cooling to room temperature, the reaction mixture was poured into water. The precipitate was collected and washed with water to give the title compound 13.0mg as a white solid. Yield 60.7%.

Melting point: 234-235°C

Mass spectrometry: 492

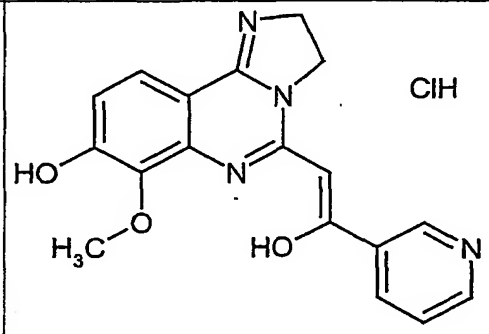
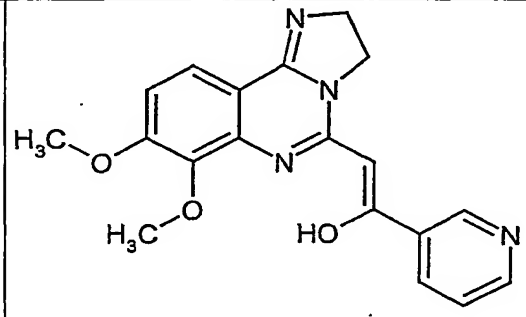
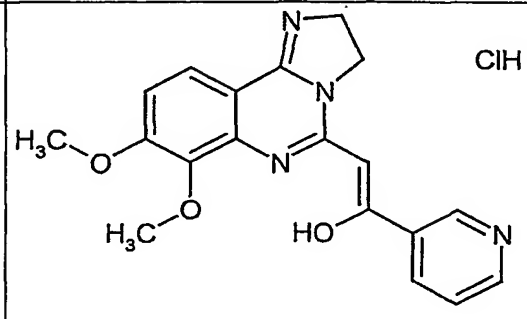
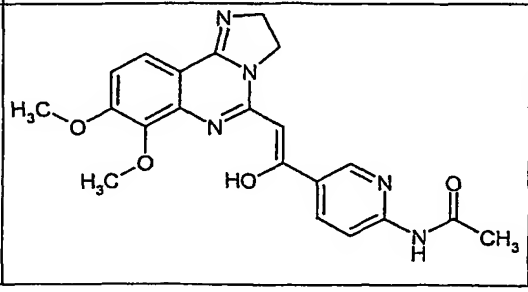
In vitro PI3K-β inhibitory activity: B

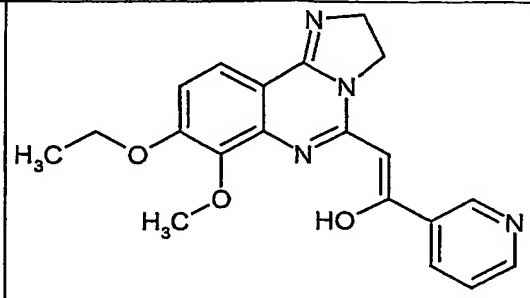
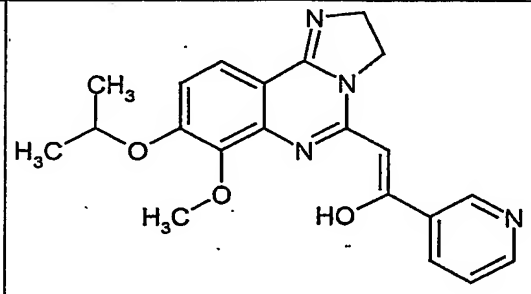
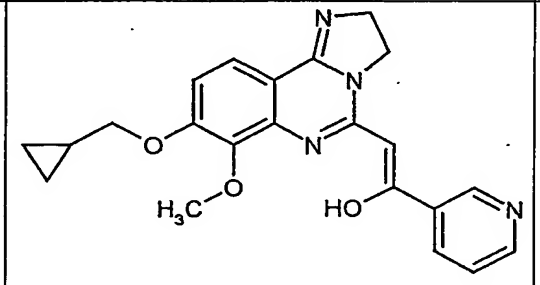
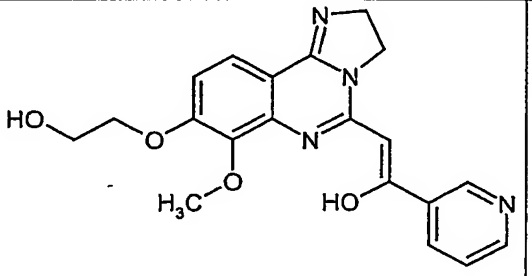
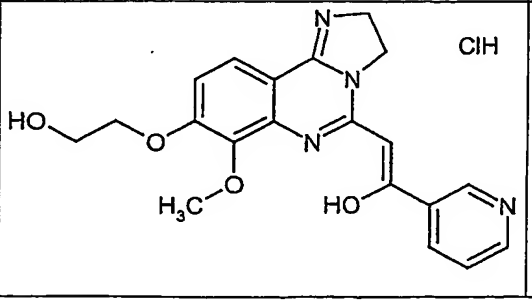
In vitro PI3K-γ inhibitory activity: A

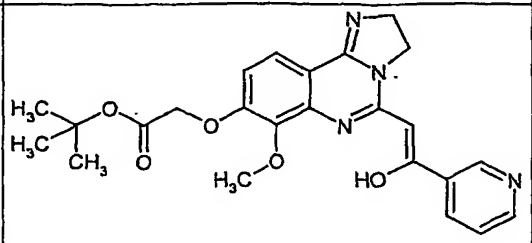
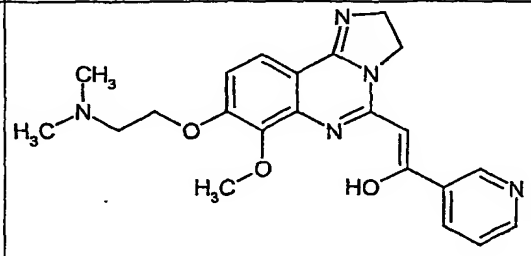
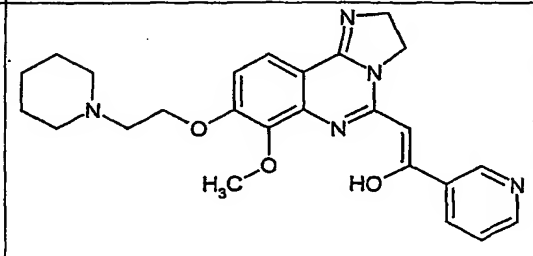
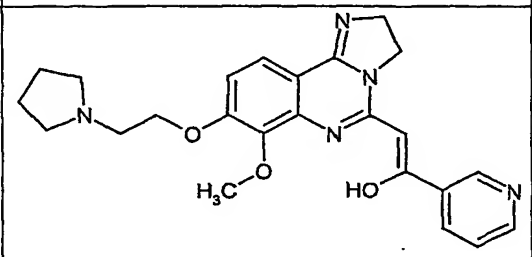
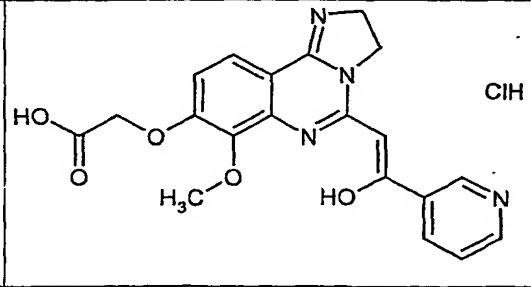
H-NMR (500MHz, DMSO-d_6) δ:2.03(quint 2H J=6.6Hz), 3.46(m 4H), 3.56(m 4H), 3.96(s 3H), 3.99(br d 2H J=8.2Hz), 4.05(br d 2H J=8.2Hz), 4.15(t 2H J=6.6Hz), 5.66(s 1H), 6.98(d J=8.8Hz), 7.50(dd 1H J=7.7Hz, 4.7Hz), 7.57(d 1H J=8.8Hz), 8.29(br d 1H J=7.7Hz), 8.67(br d 1H J=4.7Hz), 9.14(s 1H), 13.76(s 1H)

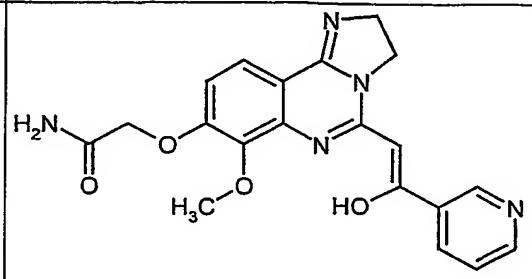
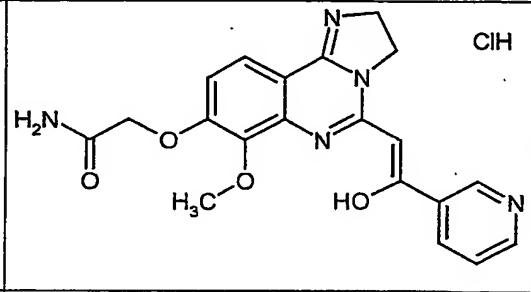
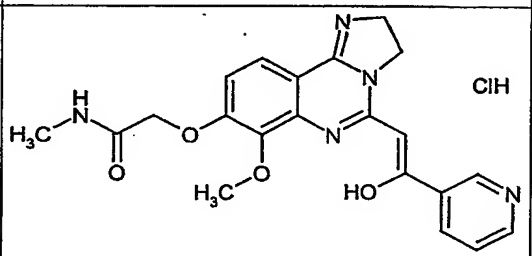
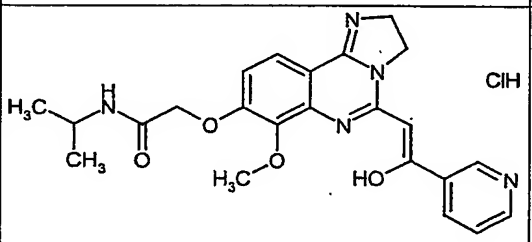
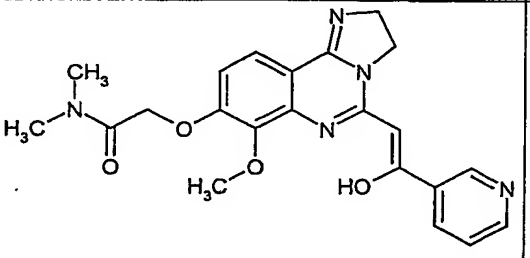
In a similar method according to the Example1-1 to 1-8 above, the compounds in Example 1-9 to 1- 210 were synthesized.

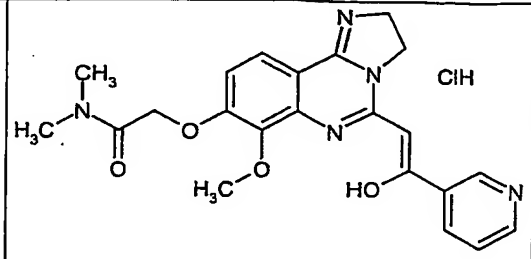
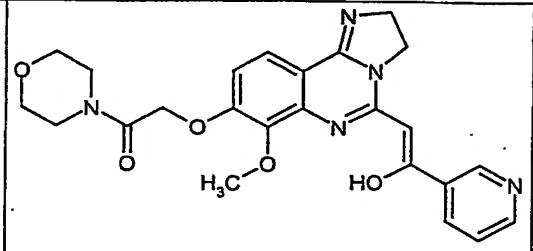
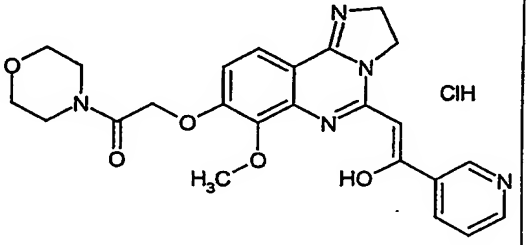
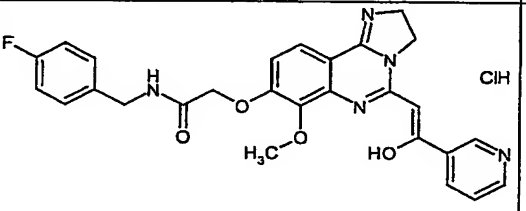
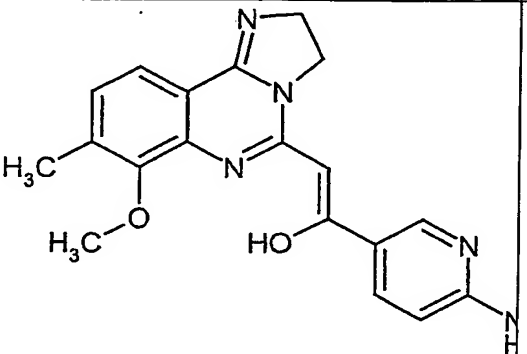
Table 1

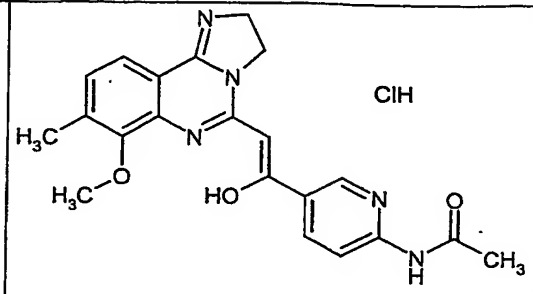
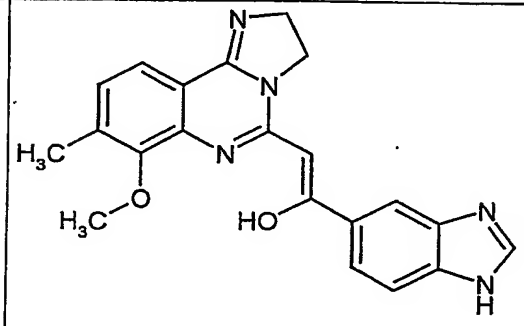
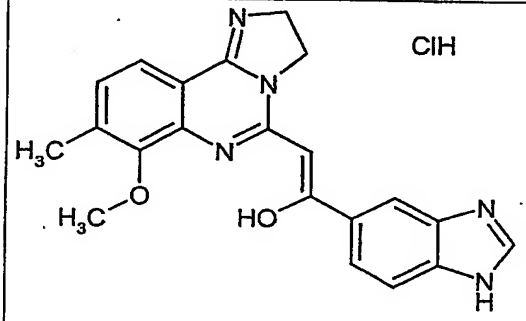
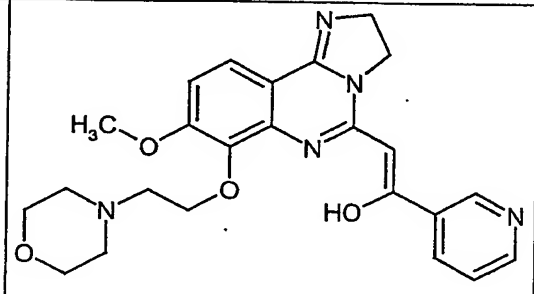
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-9		372,81	337	245(dec.)	A
1-10		350,38	351	269-270	A
1-11		386,84	351	249-250	A
1-12		407,43	408	270(dec.)	A

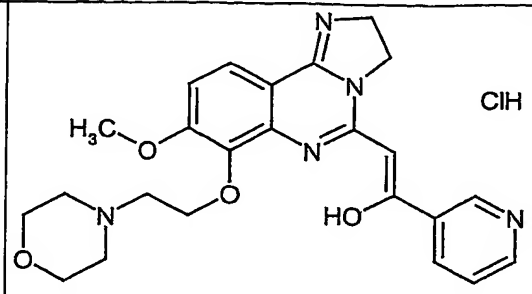
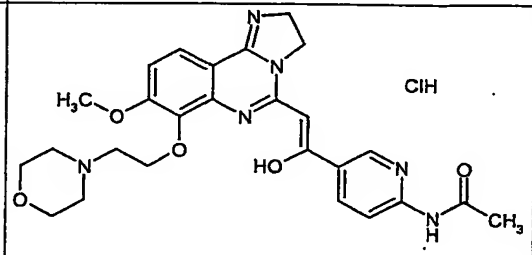
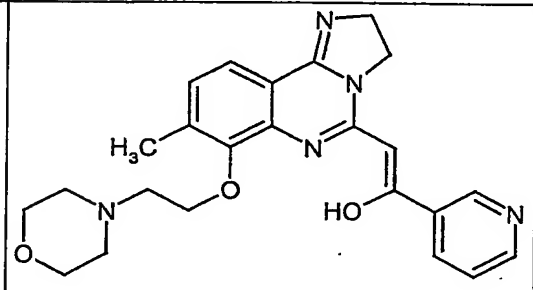
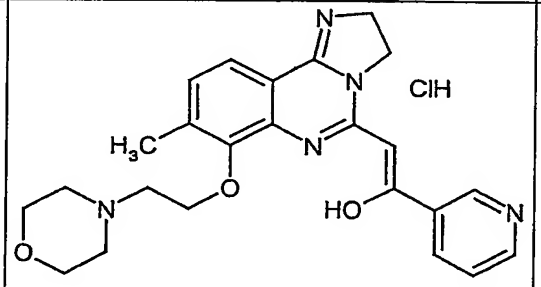
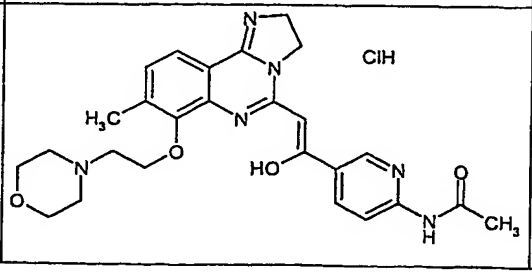
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-13		364,41	365	267-268	A
1-14		378,43	379	252-253	A
1-15		390,45	391	254(dec.)	B
1-16		380,41	381	264-265	A
1-17		416,87	381	215(dec.)	A

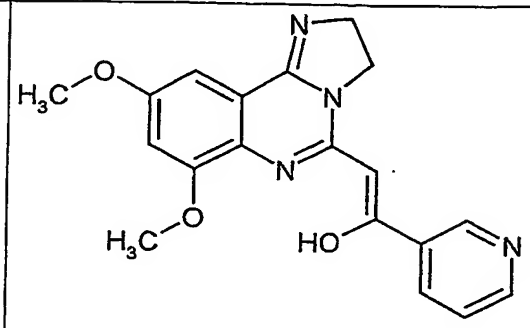
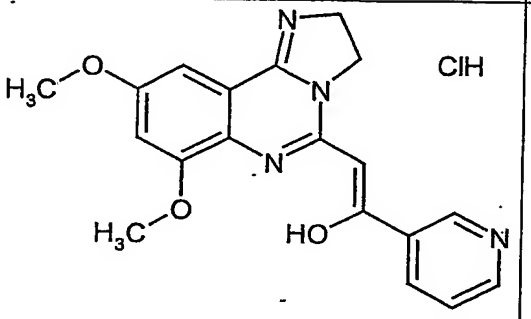
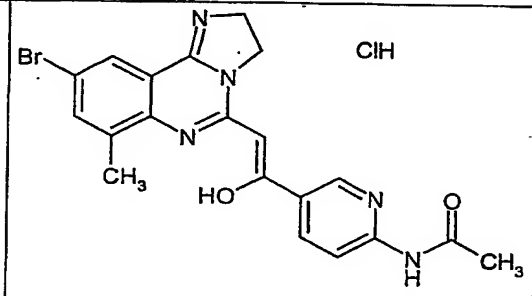
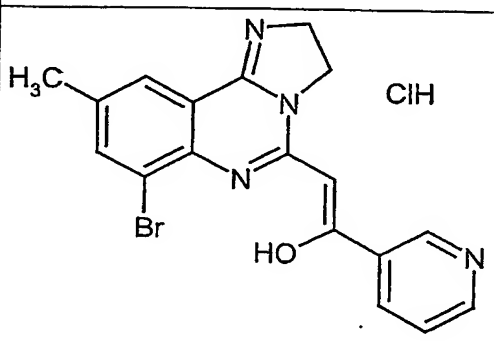
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-18		450,50	451	184-186	B
1-19		407,48	408	183-184	B
1-20		447,54	448	162-163	B
1-21		433,51	434	204-205	A
1-22		430,85	395	240(dec.)	A

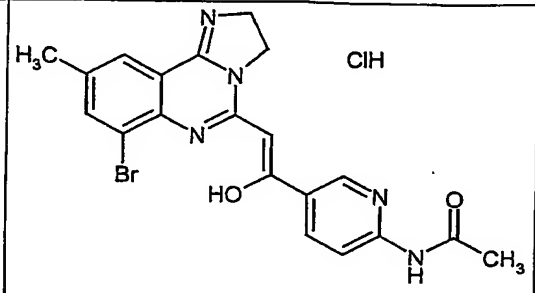
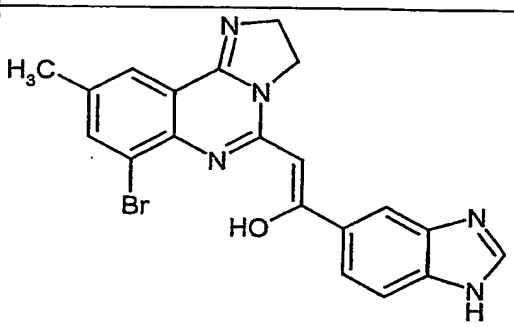
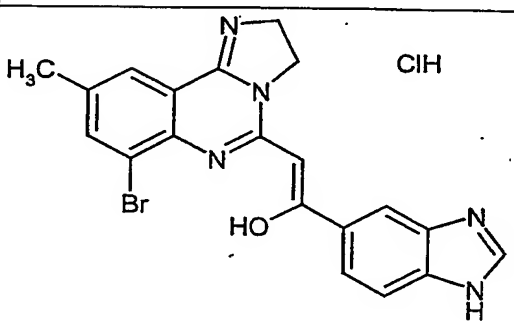
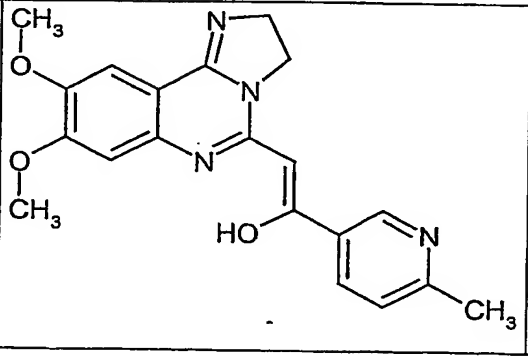
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-23		393,41	394	297-298	A
1-24		429,87	394	235(dec.)	A
1-25		443,89	408	240(dec.)	A
1-26		471,95	436	245(dec.)	A
1-27		421,46	422	241-242	A

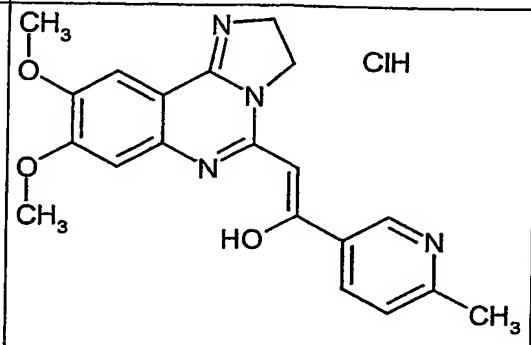
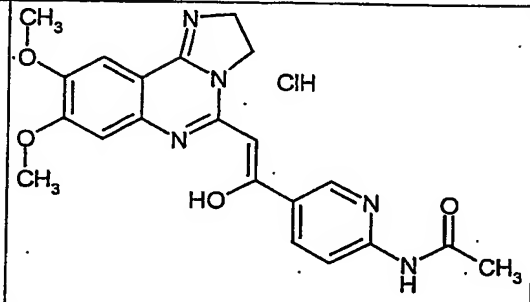
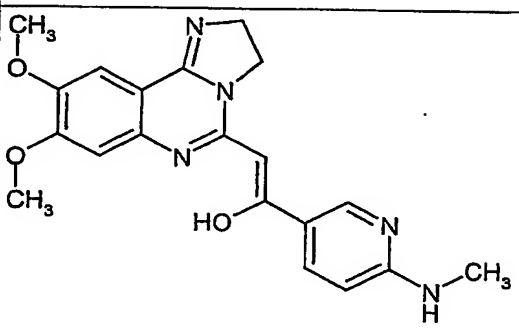
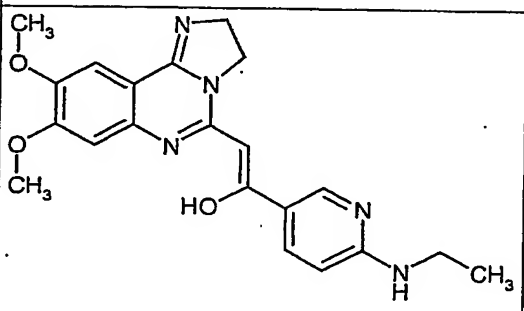
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-28		457,92	422	205(dec.)	A
1-29		463,50	464	234-235	A
1-30		499,96	464	240-241	A
1-31		537,98	502	230-231	B
1-32		391,43	392	>285	A

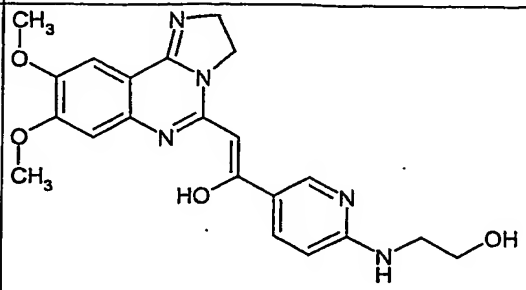
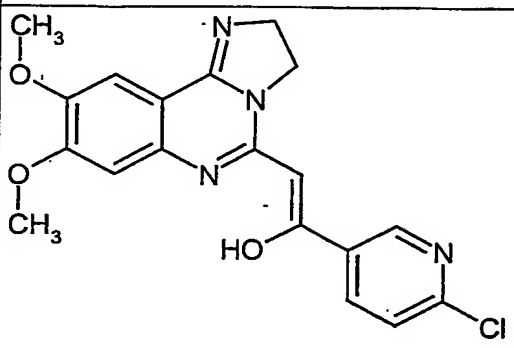
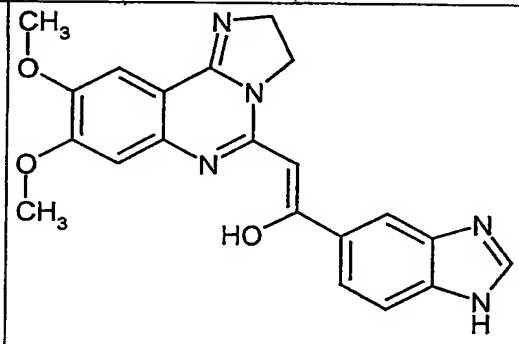
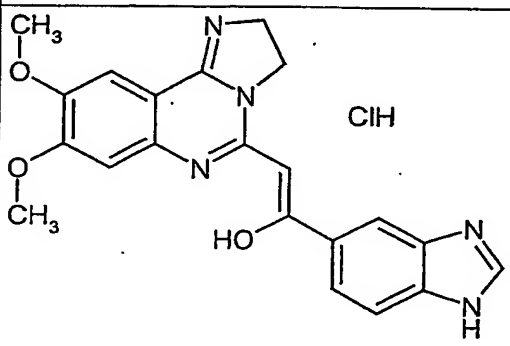
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-33		427,89	392	273	A
1-34		373,42	374	>285	A
1-35		409,88	374	270	A
1-36		449,51	450	197	A

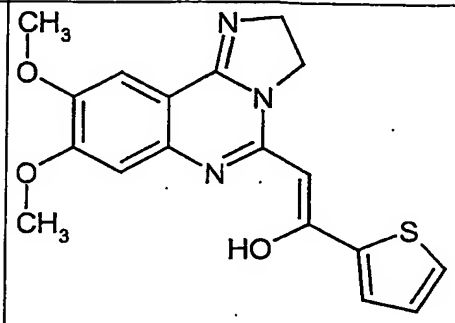
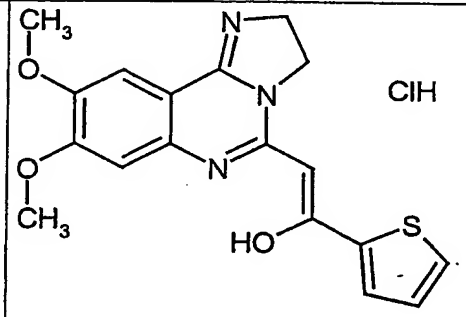
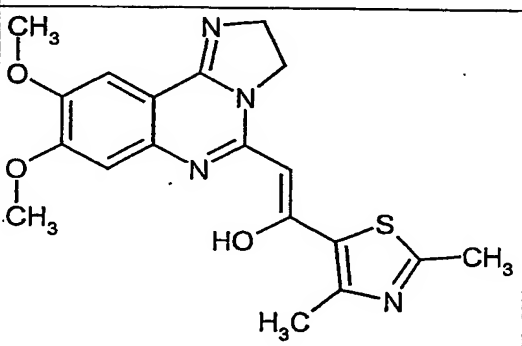
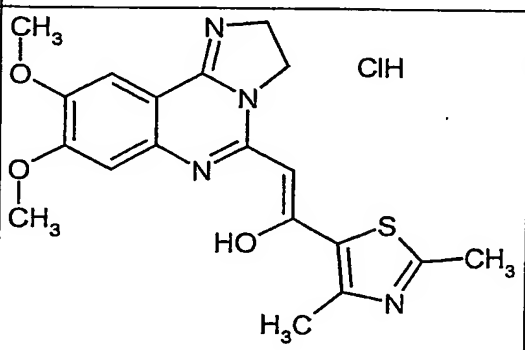
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-37		485,97	450	215	A
1-38		543,03	507	260	A
1-39		433,51	434	217	B
1-40		469,98	434	256(dec.)	B
1-41		527,03	491	271	A

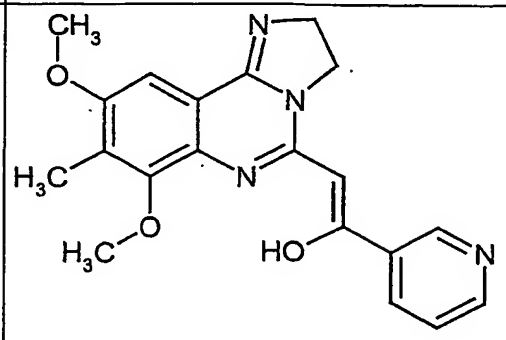
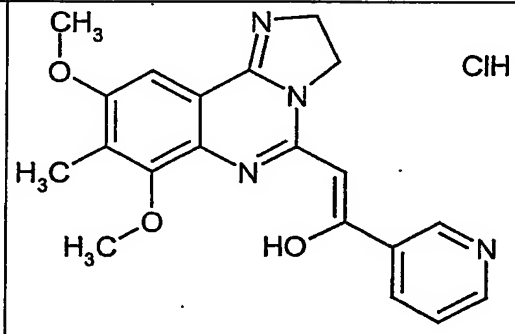
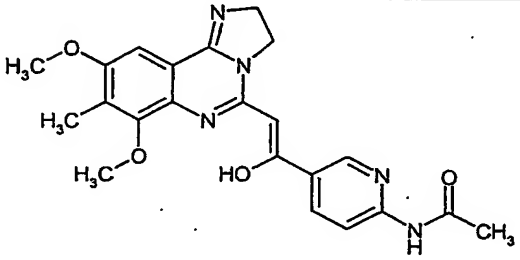
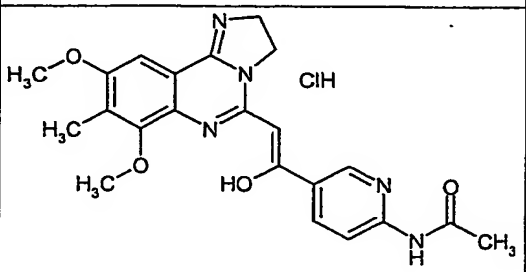
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-42		350,38	351	218	A
1-43		386,84	351	290(dec.)	A
1-44		476,76	442, 440	>290	B
1-45		419,71	385, 383	>290	B

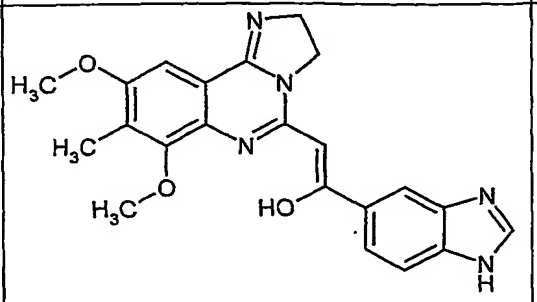
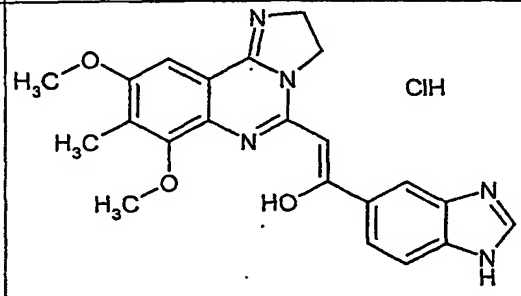
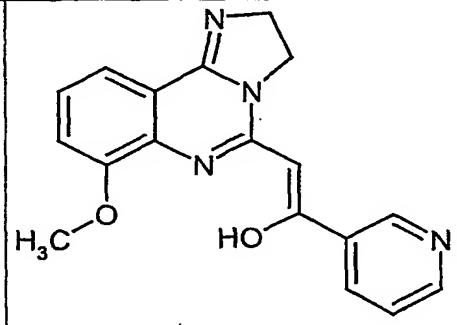
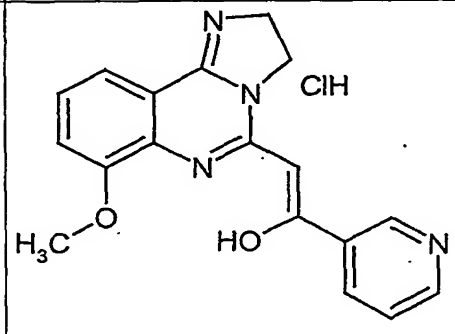
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-46		476,76	442, 440	>285	A
1-47		422,29	424, 422	>285	B
1-48		458,75	424, 422	>285	B
1-49		364,41	365	200-204	A

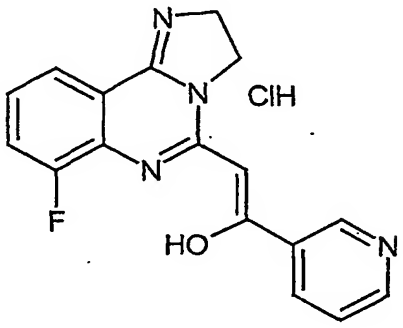
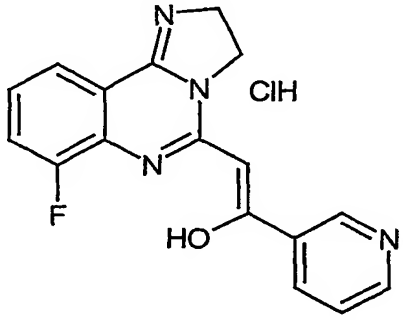
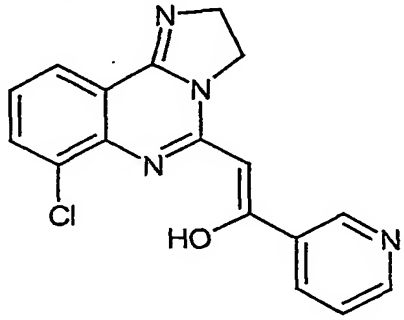
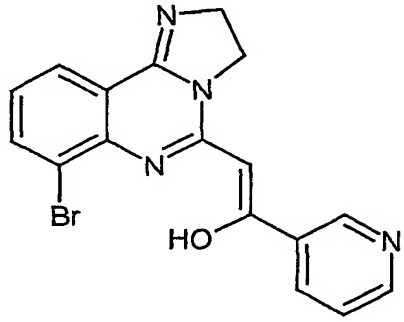
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-50		400,87	365	260(dec.)	B
1-51		443,89	408	275-280	B
1-52		379,42	380	321-325	B
1-53		393,45	394	195-198	B

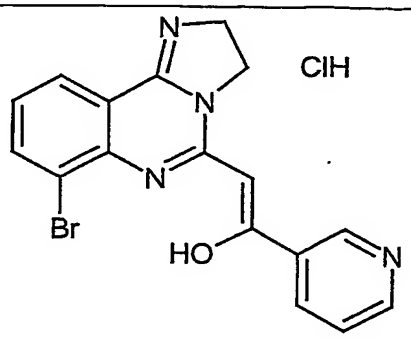
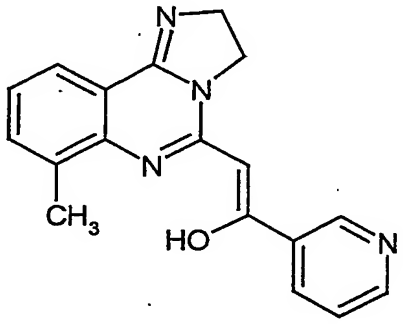
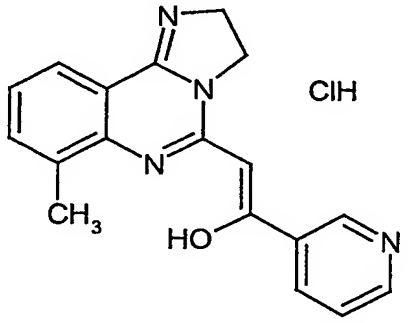
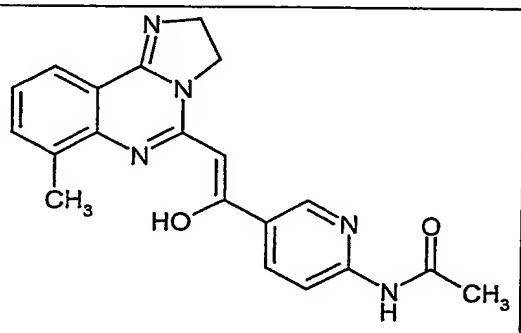
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-54		409,45	410	207	B
1-55		384,83	385	283	B
1-56		389,42	390	212-215	A
1-57		425,88	390	240(dec.)	A

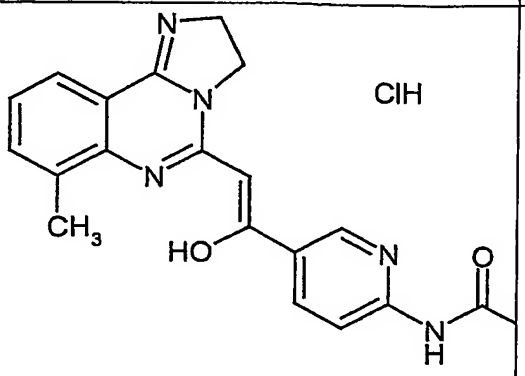
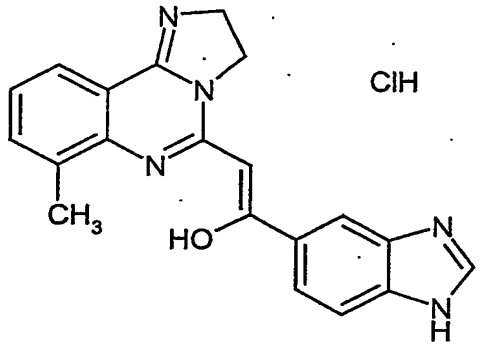
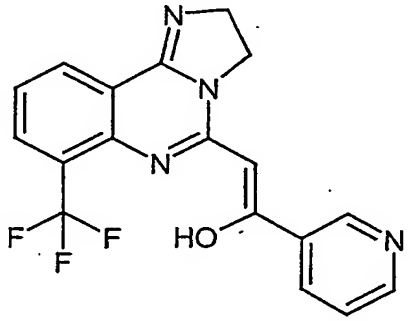
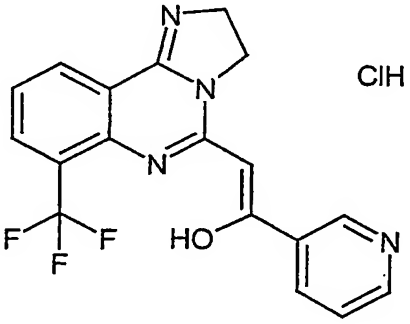
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-58		355,42	356	250	B
1-59		391,88	356	266-268	B
1-60		384,46	385	292	A
1-61		420,92	385	268-271	A

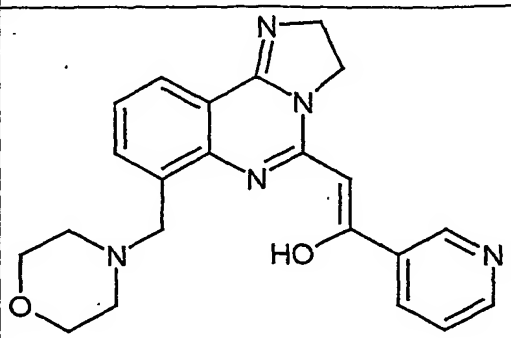
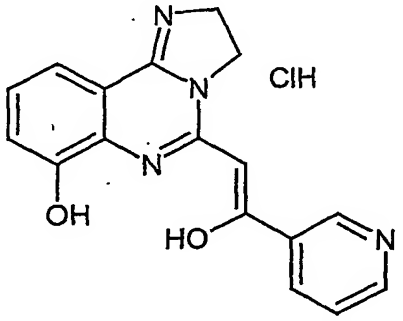
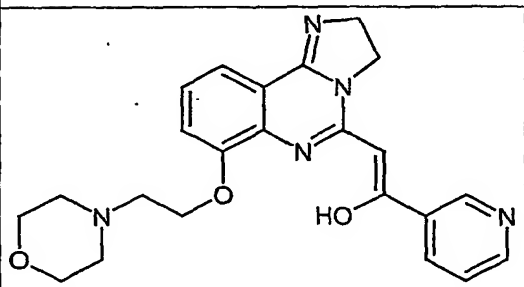
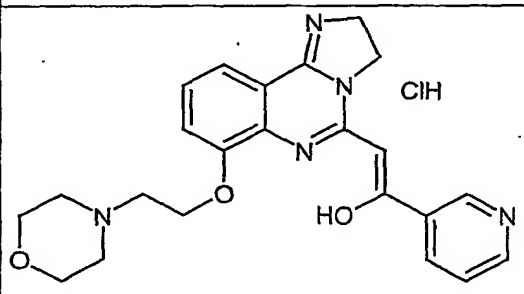
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-62		364,41	365	278	A
1-63		400,87	365	285	A
1-64		421,46	422	>285	A
1-65		457,92	422	>285	A

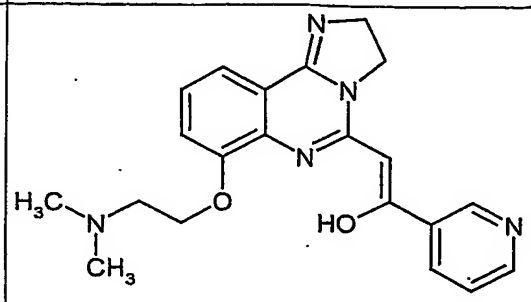
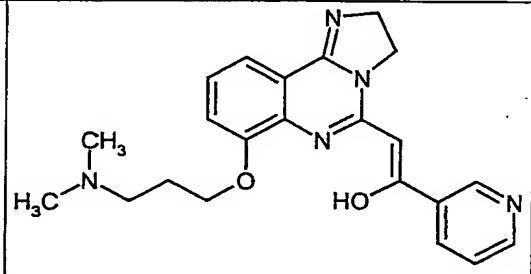
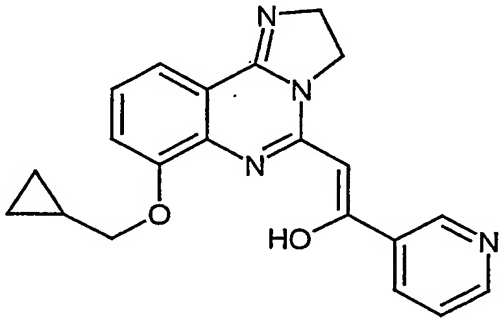
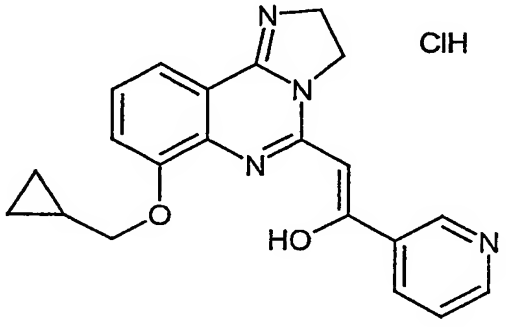
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-66		403,44	404	280	B
1-67		439,91	404	>285	B
1-68		320,35	321	275	A
1-69		356,81	321	285	A

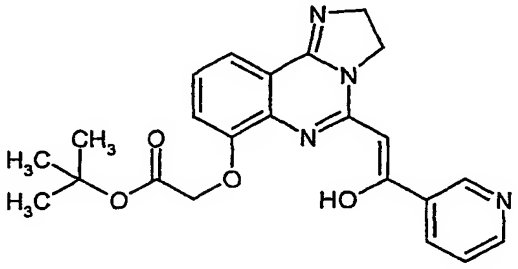
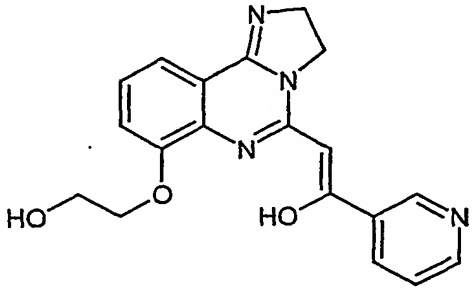
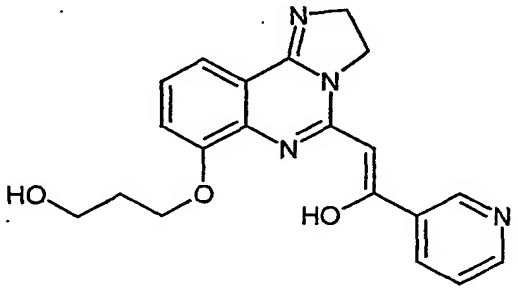
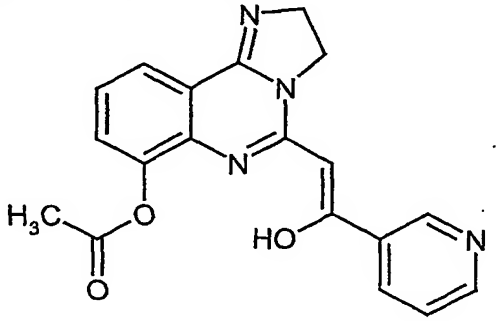
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-70		308,32	309	218	A
1-71		344,78	309	303	B
1-72		324,77	325	210(dec.)	B
1-73		369,22	371, 369	120(dec.)	B

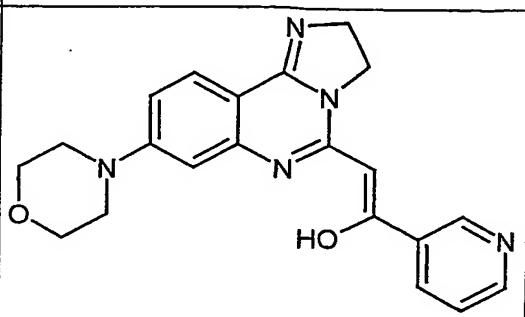
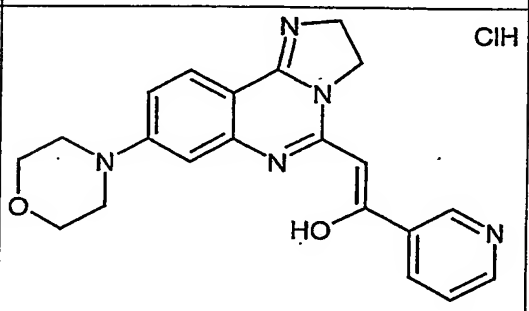
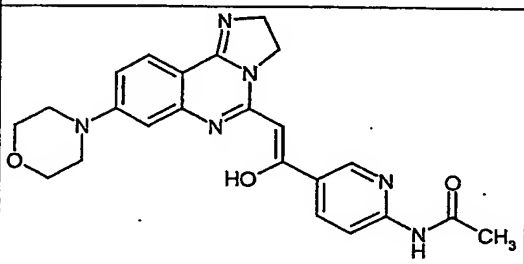
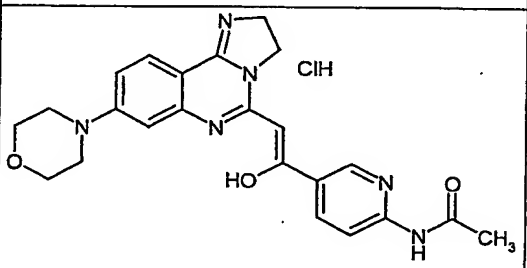
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-74		405,68	371, 369	246	B
1-75		304,35	305	248	B
1-76		340,82	305	>290	B
1-77		361,41	362	>285	A

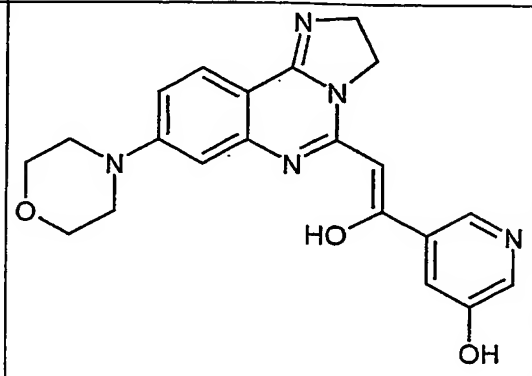
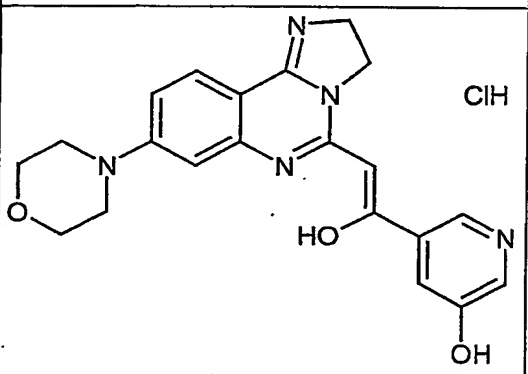
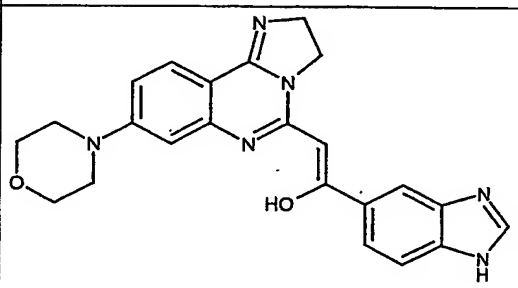
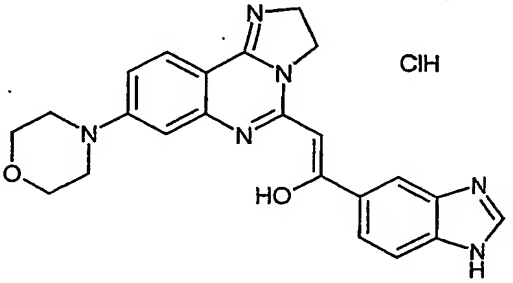
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-78		397,87	362	>285	A
1-79		379,85	344	>285	A
1-80		358,33	359	275	B
1-81		394,79	359	>290	B

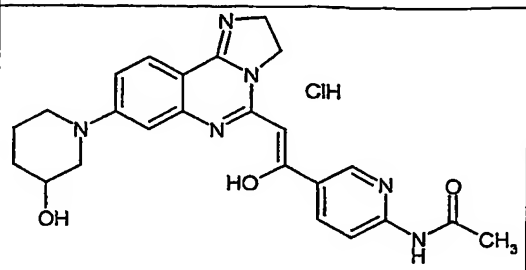
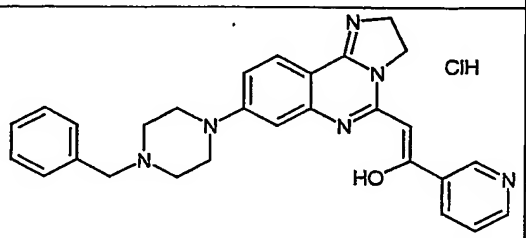
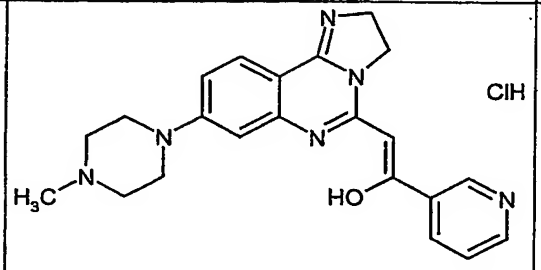
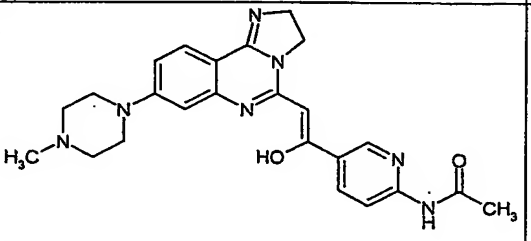
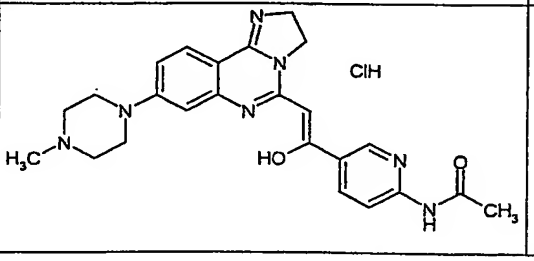
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-82		389,46	390	198 - 202 (dec.)	B
1-83		342,79	307	>250	B
1-84		419,49	420	195-196	B
1-85		455,95	420	261-262	B

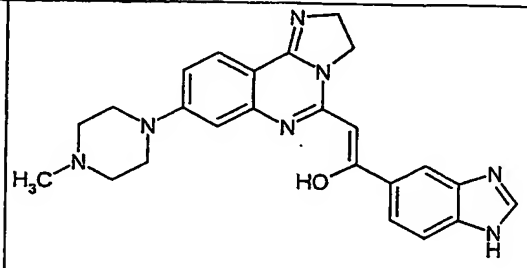
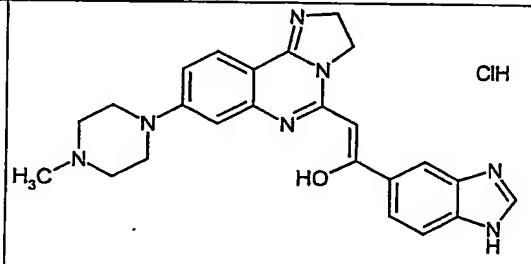
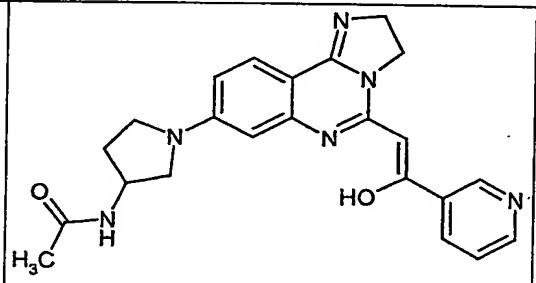
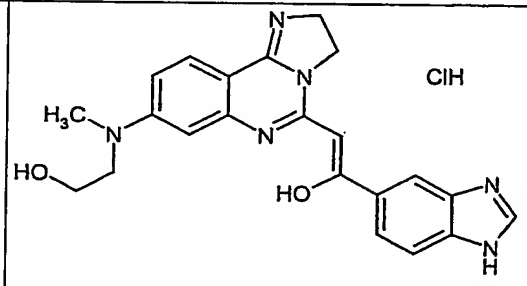
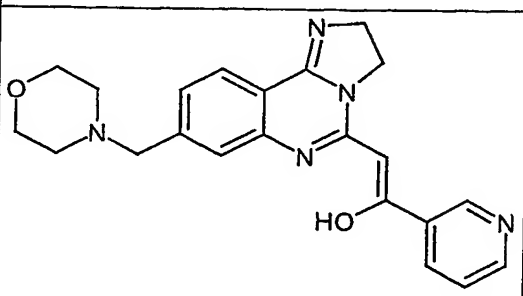
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-86		377,45	378	186-187	B
1-87		391,48	392	235(dec.)	B
1-88		360,42	361	203(dec.)	B
1-89		396,88	361	>300	B

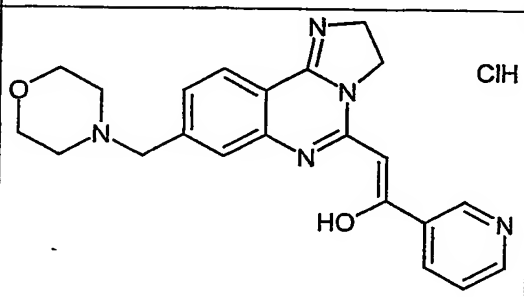
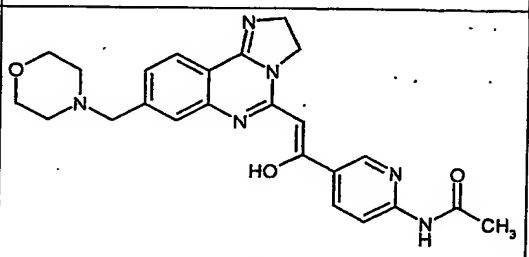
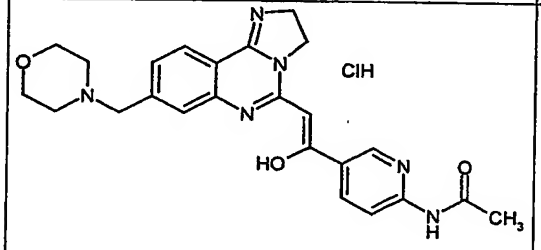
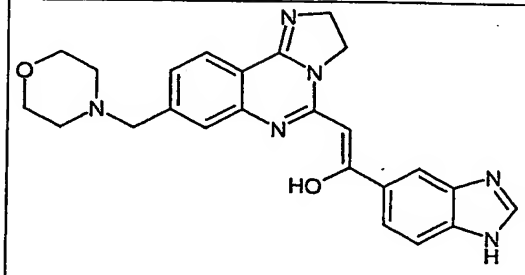
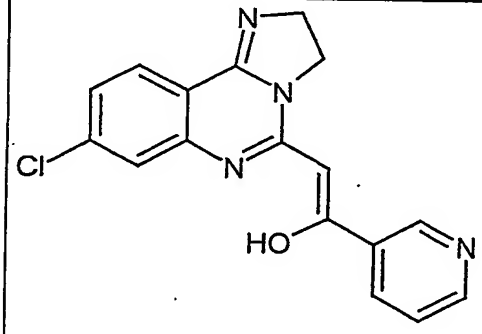
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-90		420,47	421	222-223	A
1-91		350,38	351	211-212	B
1-92		364,41	365	203-205	A
1-93		348,36	349	225-226	B

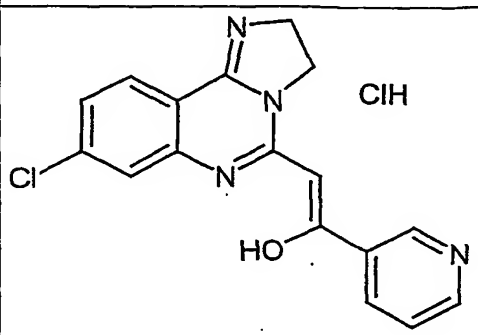
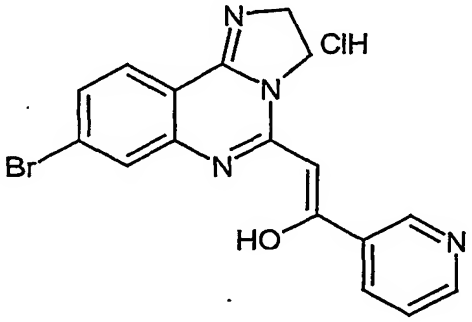
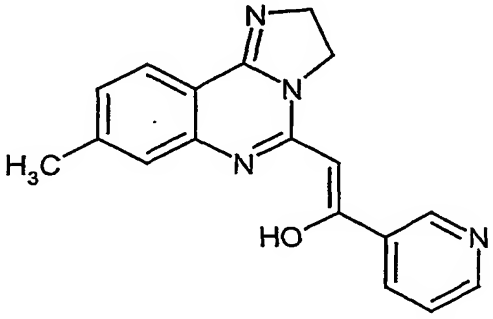
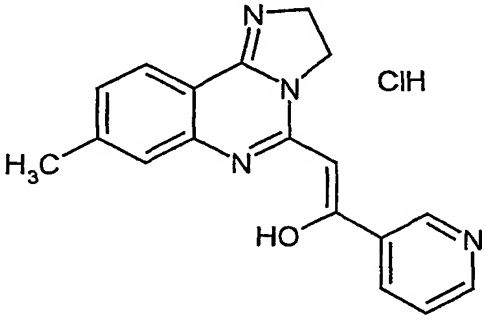
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-94		375,43	376	282	B
1-95		411,89	376	>300	B
1-96		432,49	433	269(dec.)	A
1-97		468,95	433	246	A

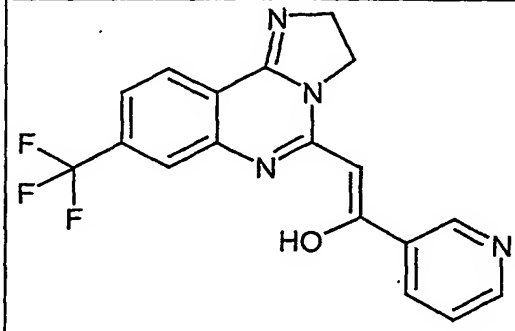
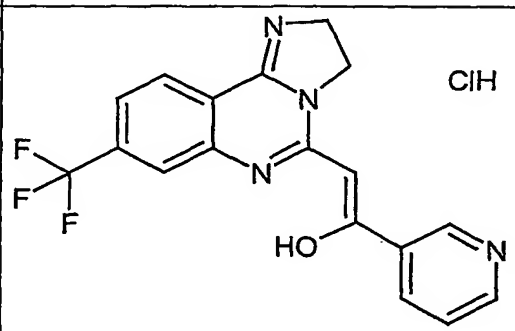
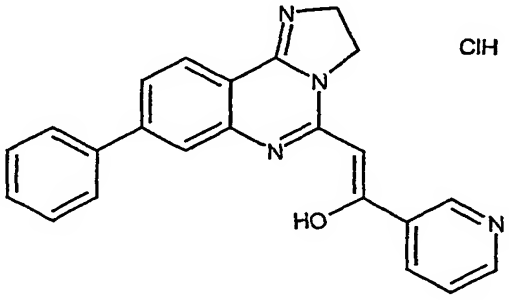
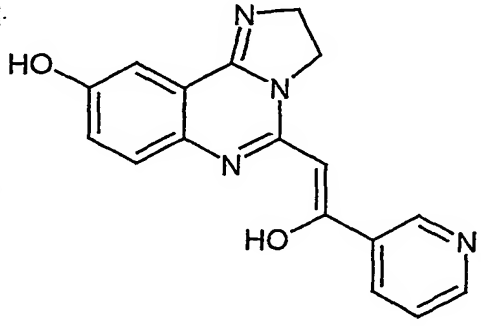
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-98		391,43	392	337(dec.)	A
1-99		427,89	392	312(dec.)	A
1-100		414,47	415	232	A
1-101		450,93	415	286(dec.)	A

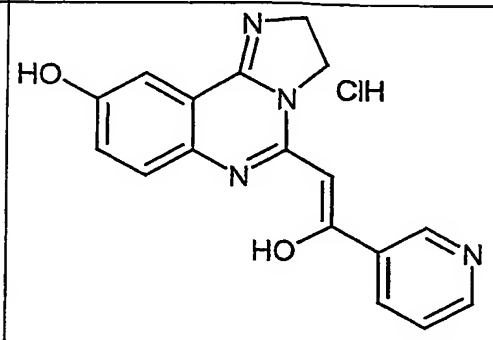
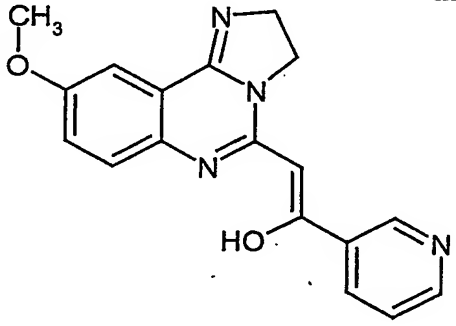
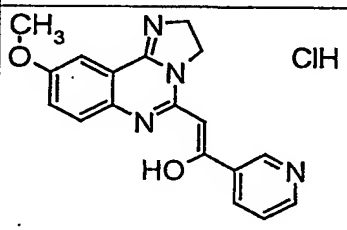
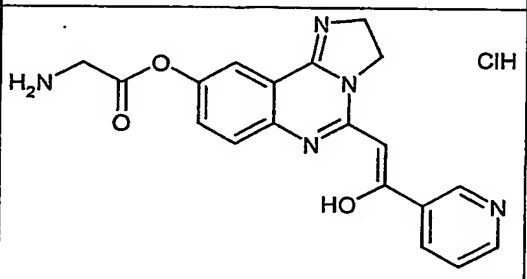
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-102		482,97	447	238(dec.)	B
1-103		501,04	466	257	B
1-104		424,94	389	288	B
1-105		445,53	446	292(dec.)	B
1-106		481,99	446	280(dec.)	B

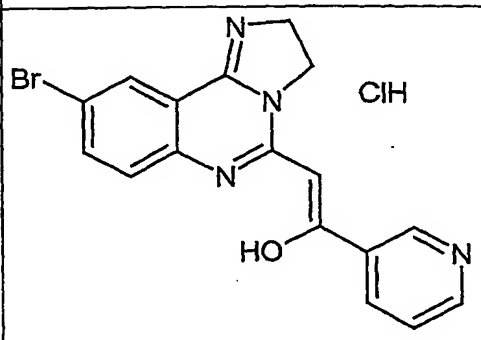
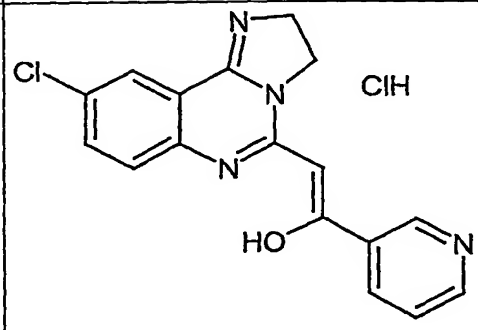
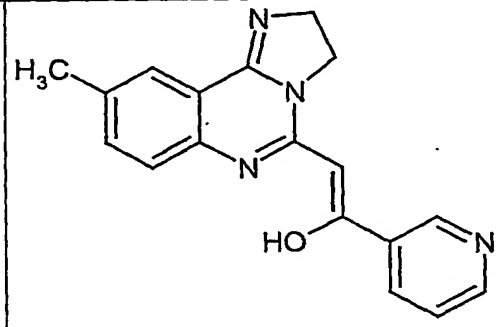
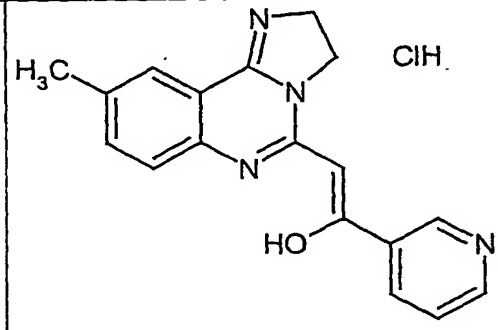
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-107		427,51	428	207	A
1-108		463,97	428	>300	B
1-109		416,49	416		A
1-110		438,92	403	231(dec.)	B
1-111		389,46	390	204	B

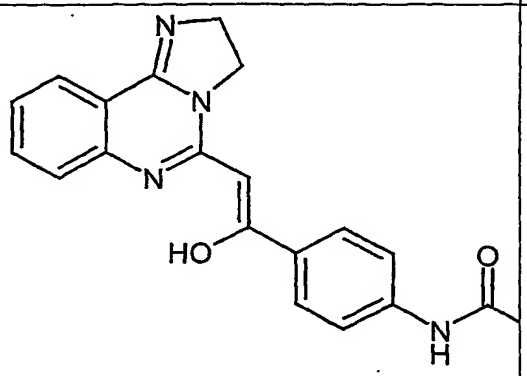
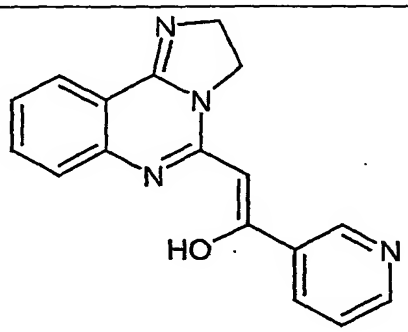
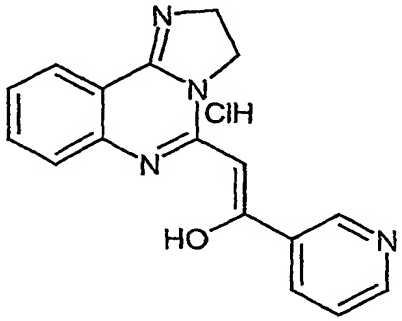
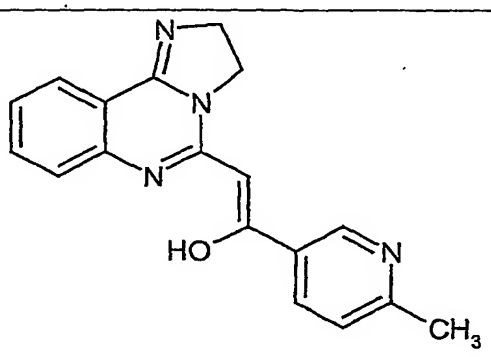
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-112		425,92	390	242	B
1-113		446,51	447	245	B
1-114		482,97	447	260	B
1-115		428,50	429	219	B
1-116		324,77	325	226	B

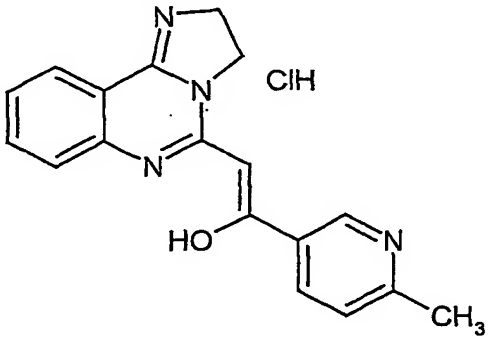
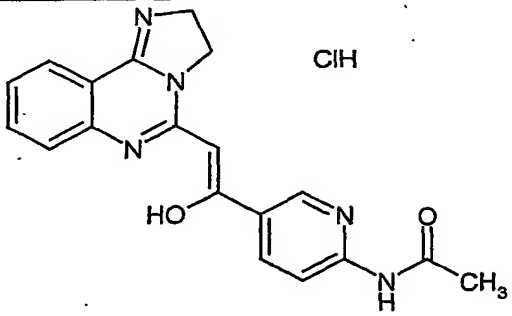
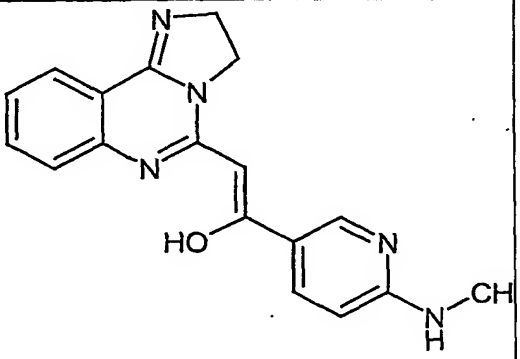
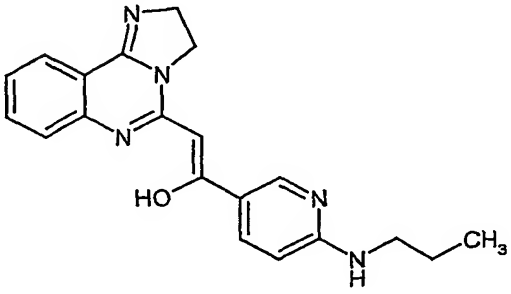
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-117		361,23	326	280(dec.)	B
1-118		405,68	371, 369	233	B
1-119		304,35	305	224	B
1-120		340,82	305	>330	B

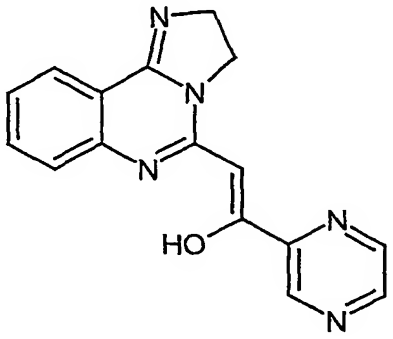
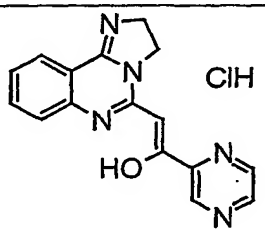
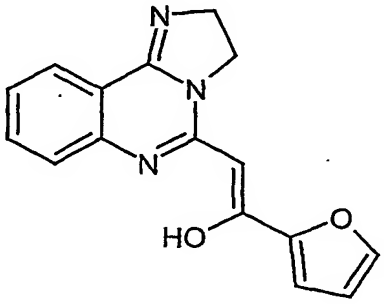
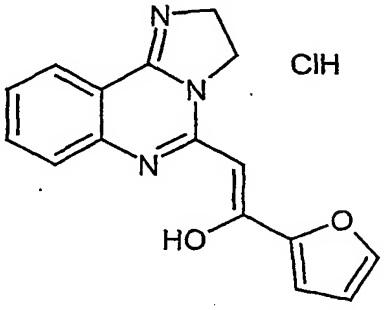
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-121		358,33	359	264	C
1-122		394,79	359	321	B
1-123		402,89	367	>300	B
1-124		306,33	307	302-303	B

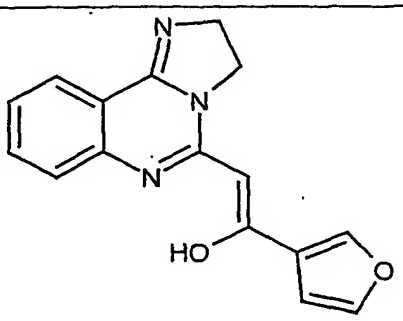
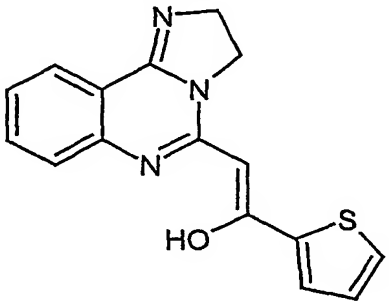
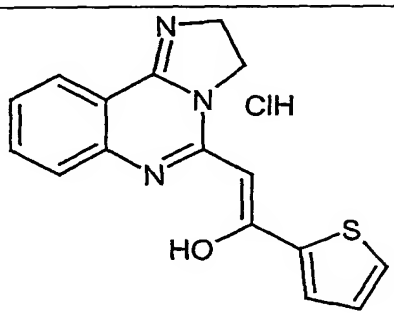
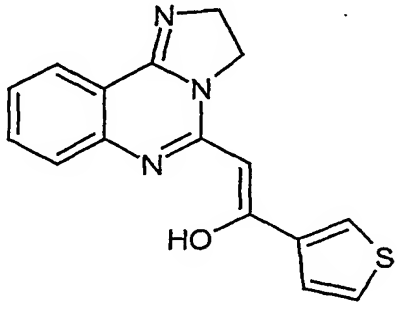
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-125		342,79	307	>300	A
1-126		320,35	321	199	B
1-127		356,81	321	>300	B
1-128		399,84	364	>300	A

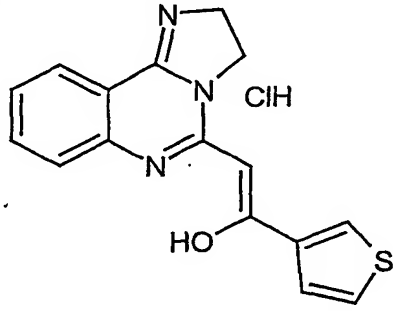
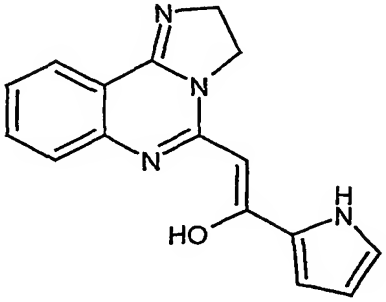
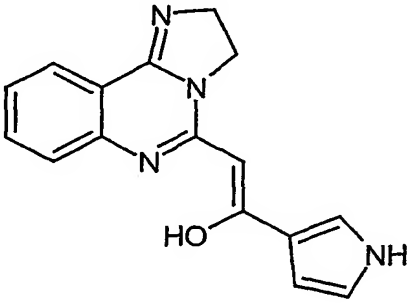
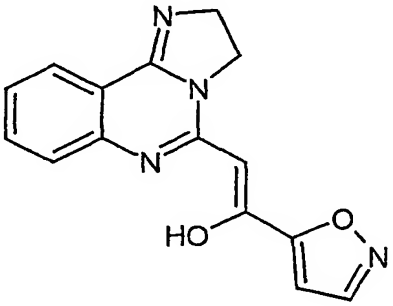
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-129		405,68	371, 369	>330	B
1-130		361,23	326	>330	B
1-131		304,35	305	212	B
1-132		340,82	305	>290	B

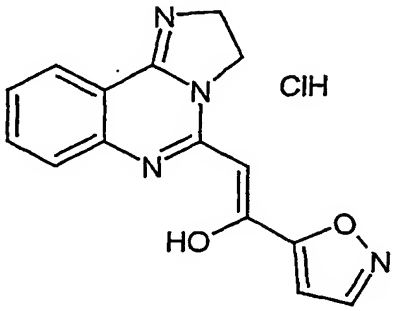
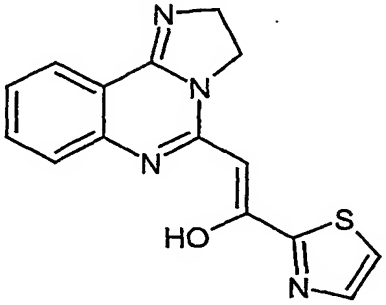
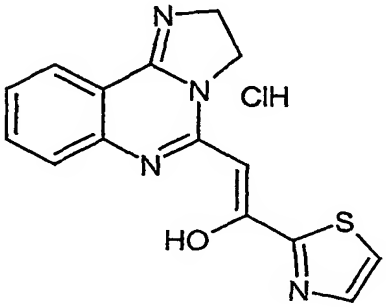
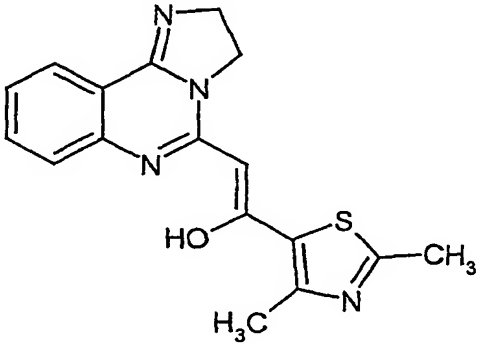
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-133		346,39	347	>300	B
1-134		290,33	291	202	B
1-135		326,79	291	260(dec.)	B
1-136		304,35	305	217-219	B

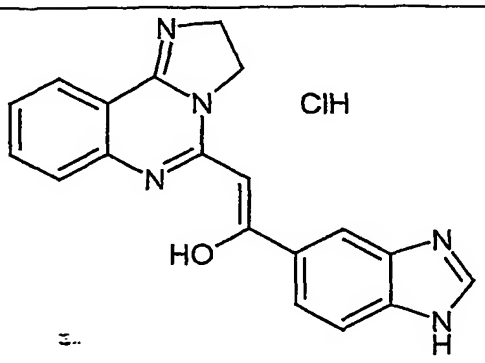
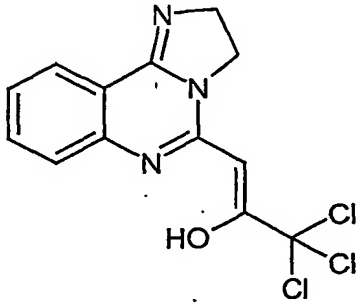
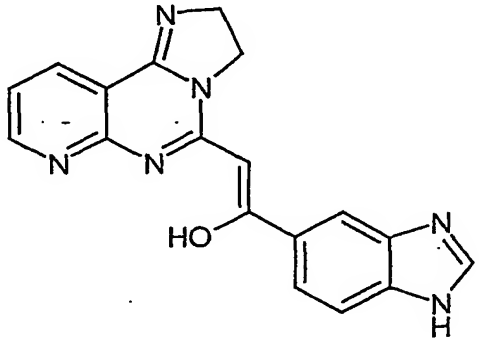
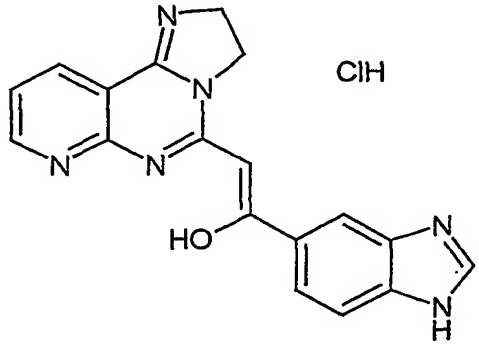
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-137		340,82	305	>300	B
1-138		383,84	348	327	A
1-139		319,37	320	232-237	A
1-140		347,42	348	197	B

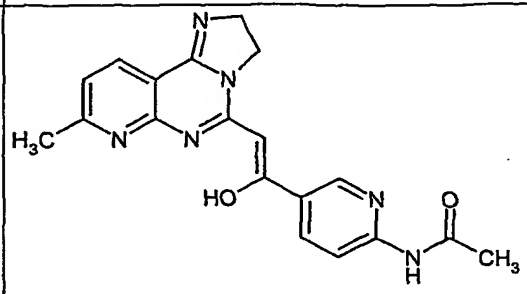
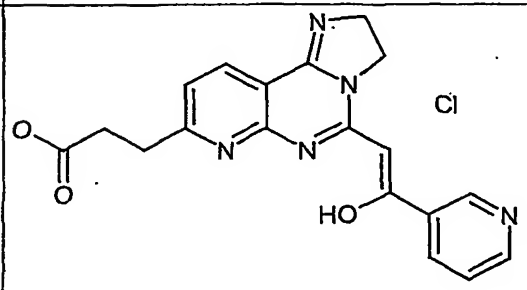
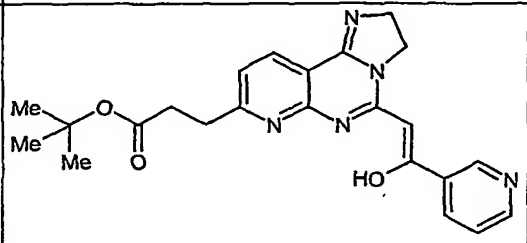
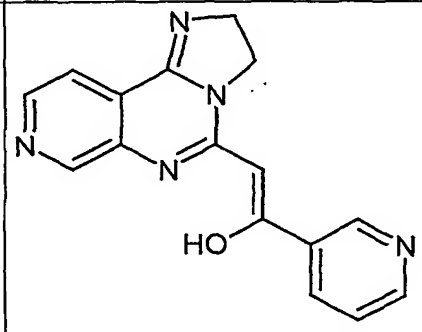
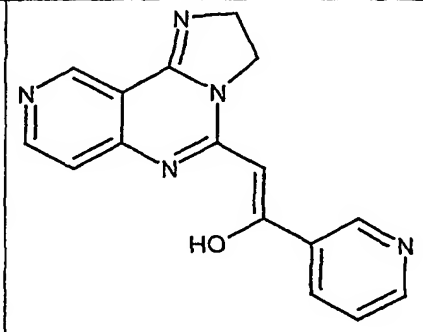
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-141		291,31	292	233-235	B
1-142		327,78	292	217-222	B
1-143		279,30	280	192	B
1-144		315,76	280	>300	B

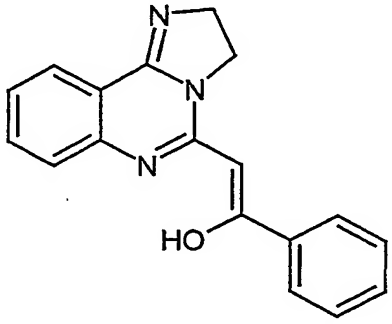
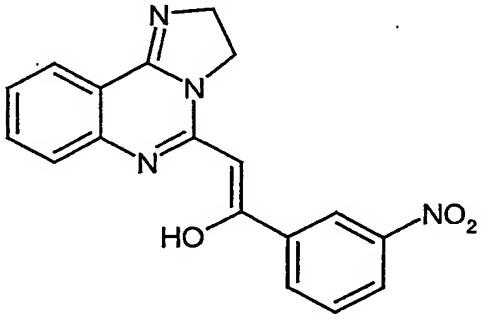
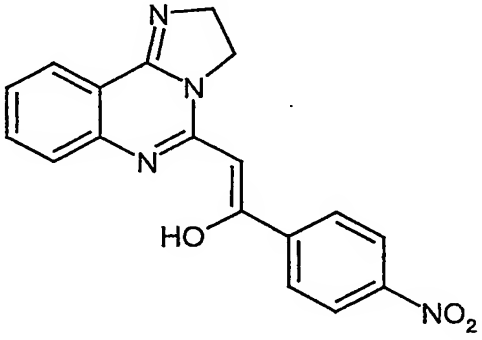
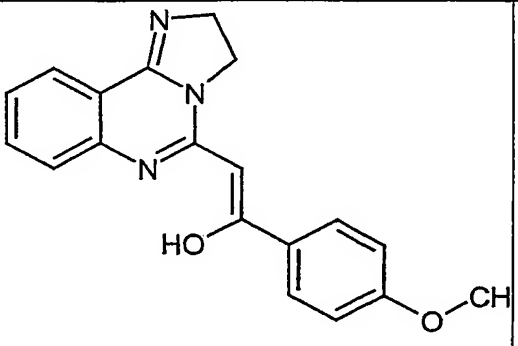
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-145		279,30	280	155-156	B
1-146		295,37	296	193	A
1-147		331,83	296	>300	A
1-148		295,37	296	182-183	B

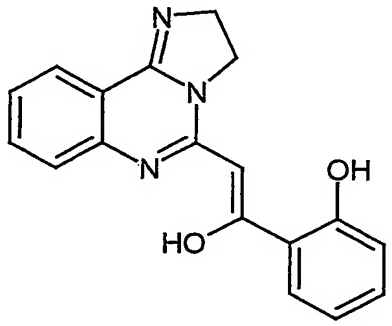
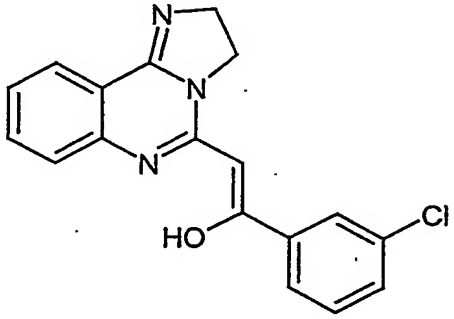
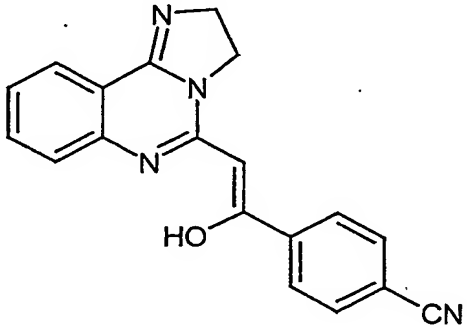
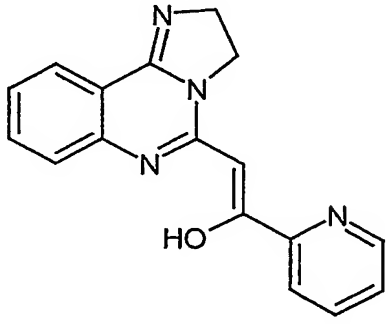
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-149		331,83	296	>300	A
1-150		278,32	279	247	B
1-151		278,32	279	247-249	A
1-152		280,29	281	148	B

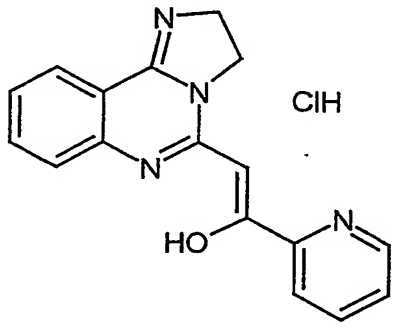
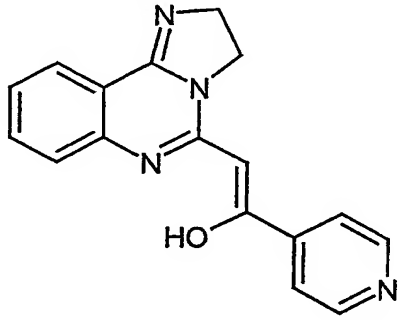
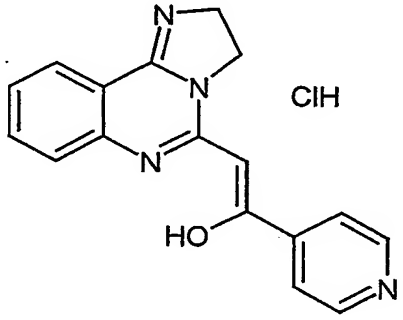
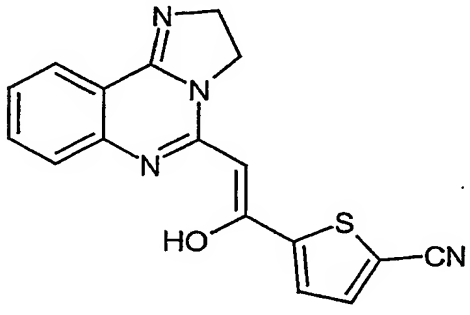
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-153		316,75	281	245(dec.)	B
1-154		296,35	297	208-210	A
1-155		332,81	297	> 300	B
1-156		324,41	325	222	A

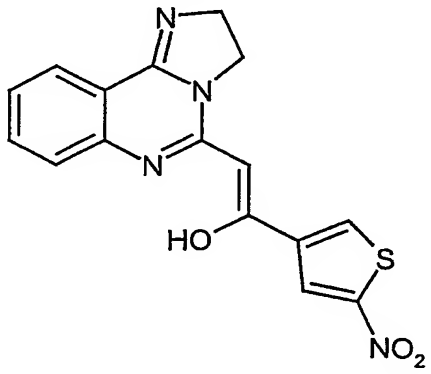
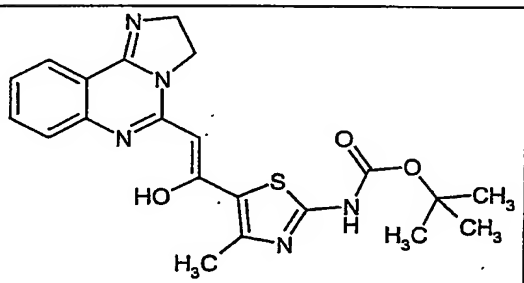
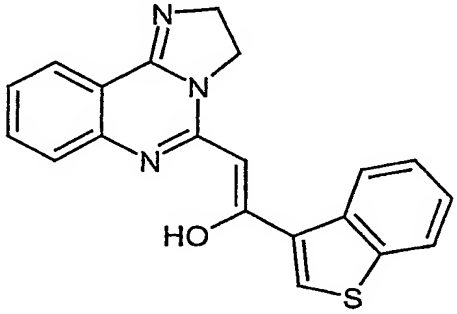
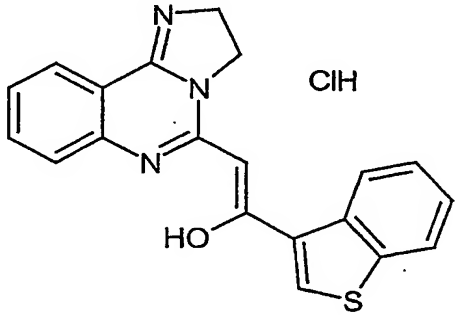
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-157		365,83	330	>300	B
1-158		330,60	330	190(dec.)	B
1-159		330,35	331	>300	A
1-160		366,81	331	247(dec.)	B

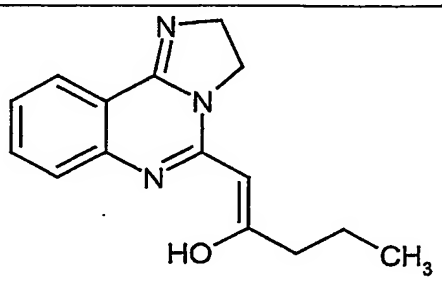
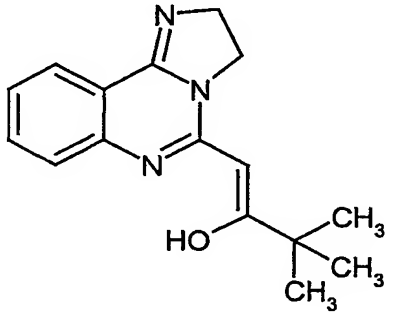
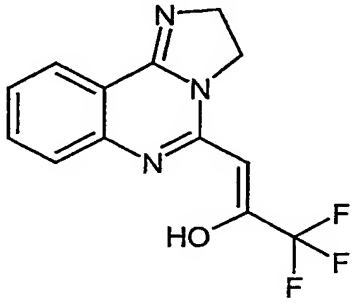
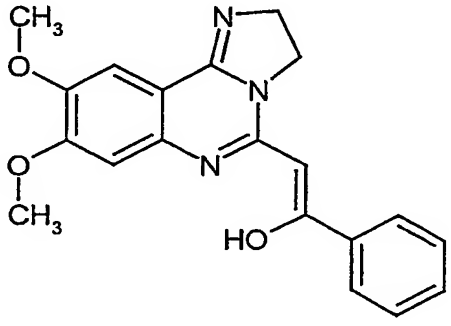
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-161		362,39	363	>300	B
1-162		399,84	400	>300	B
1-163		419,49	420	200	B
1-164		291,31	292	230	B
1-165		291,31	292	250	B

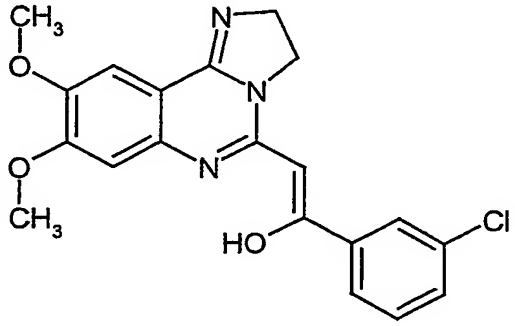
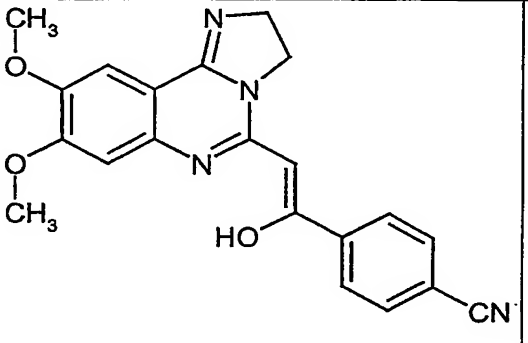
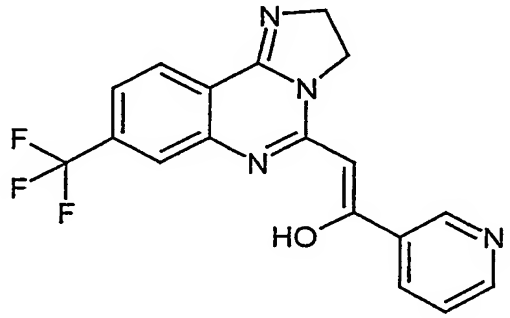
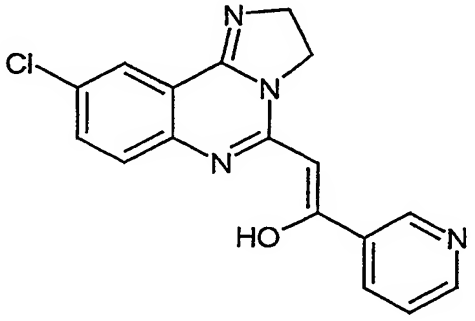
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-166		289,34	290	130-139	C
1-167		334,34	335	276	D
1-168		334,34	335	240-248	D
1-169		319,37	320	212-214	D

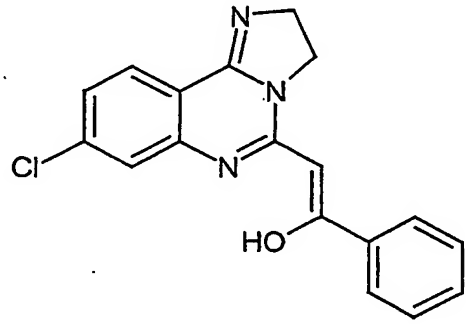
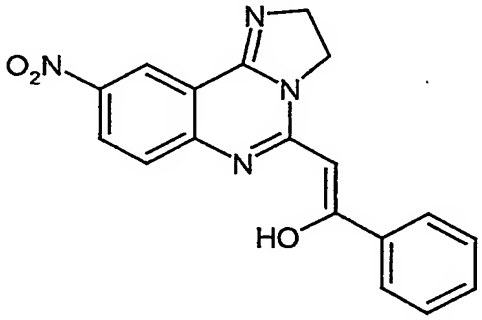
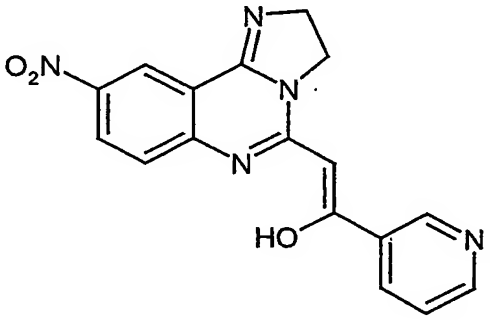
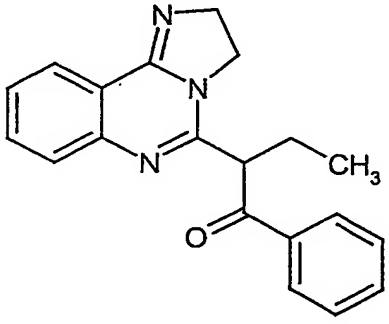
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-170		305,34	306	252-256	D
1-171		323,78	324	224-227	D
1-172		314,35	315	260-264	D
1-173		290,33	291	195	C

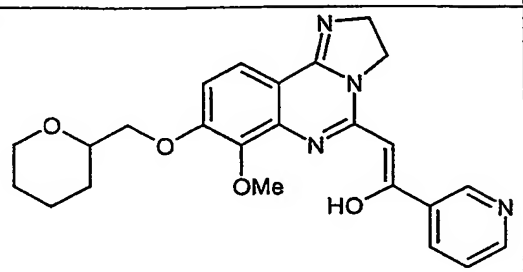
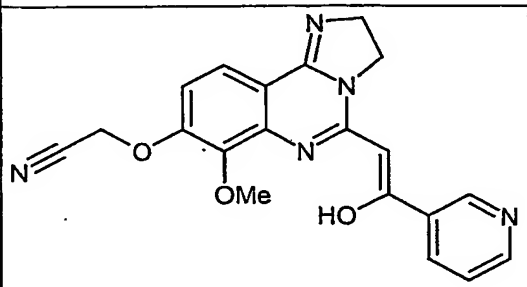
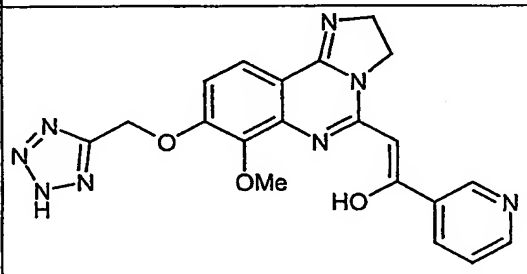
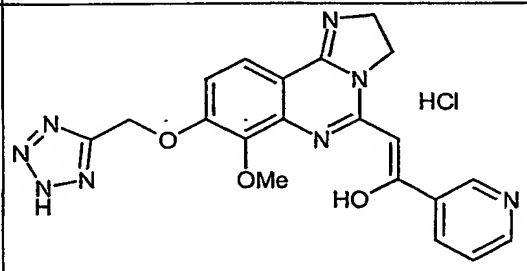
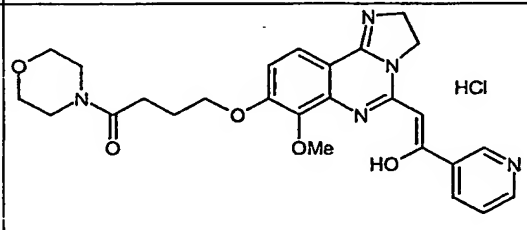
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-174		326,79	291	235-240	C
1-175		290,33	291	204-205	B
1-176		326,79	291	235(dec.)	B
1-177		320,38	321	256	C

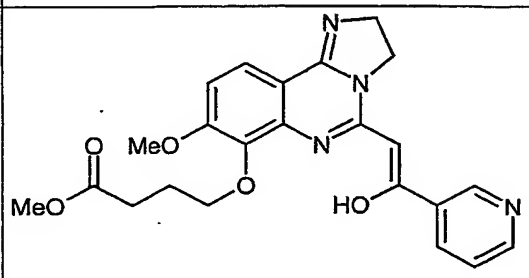
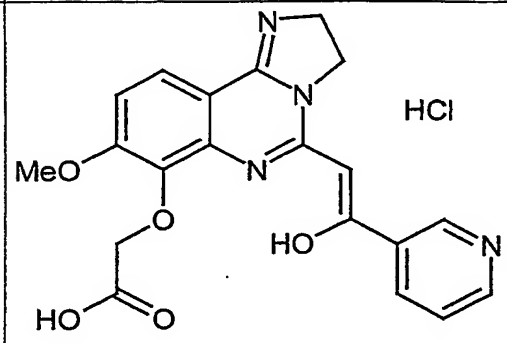
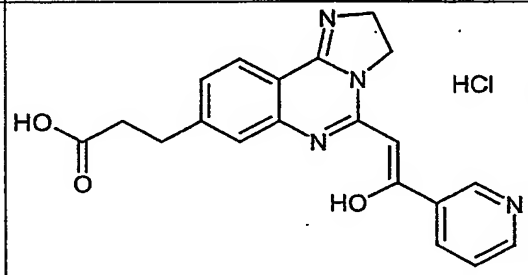
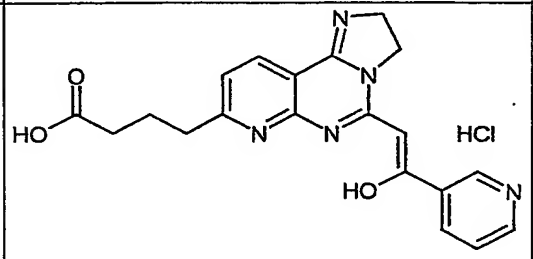
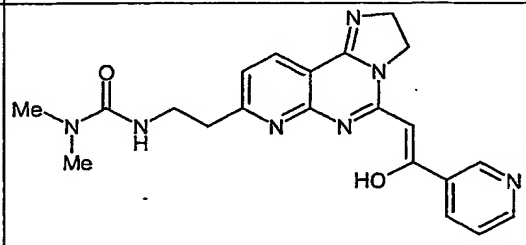
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-178		340,36	341	255-258	D
1-179		425,51	426	>300	D
1-180		345,43	346	220-225	D
1-181		381,89	346	>300	D

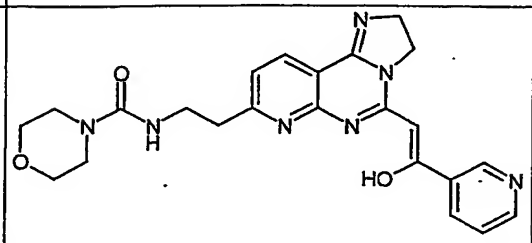
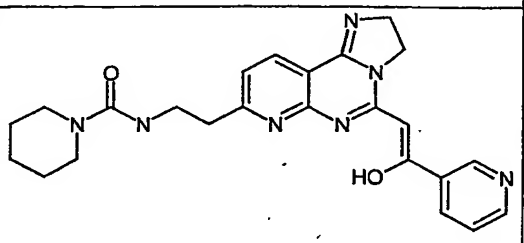
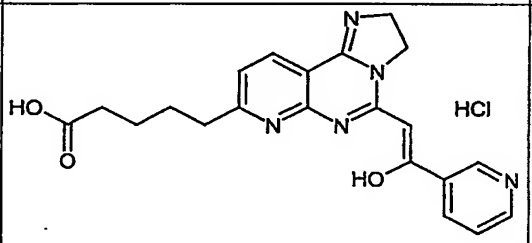
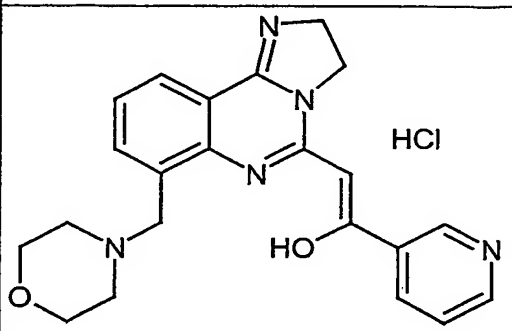
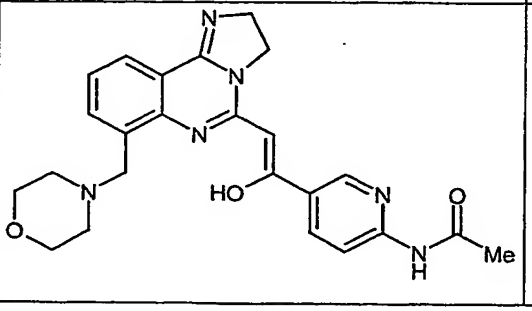
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-182		255,32	256	113	D
1-183		269,35	270	134-138	C
1-184		281,24	282	240	C
1-185		349,39	350	249-252	C

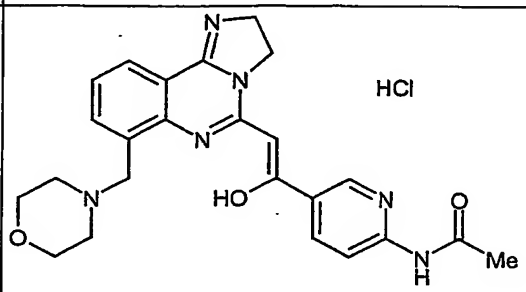
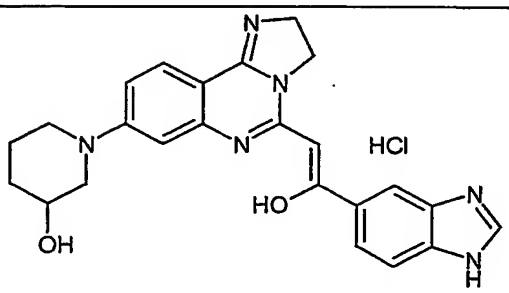
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-186		383,84	384	257-259	D
1-187		374,40	375	307-308	D
1-188		358,33	359	264	C
1-189		324,77	325	260	C

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-190		323,78	324	186-188	C
1-191		334,34	335	259-262	D
1-192		335,32	336	306	C
1-193		317,39	318	156-160	D

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-194		434,50	435	233-234	A
1-195		375,39	376	284-285	A
1-196		418,42	419	229-231	A
1-197		454,88	419	217-218	A
1-198		528,01	492	215-216	A

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-199		436,47	437	178-179	A
1-200		430,85	395	286(dec.)	B
1-201		398,85	363	273(dec.)	A
1-202		413,87	378	285(dec.)	B
1-203		405,46	406	228	B

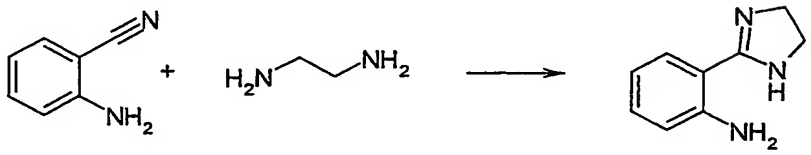
Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-204		447,50	448	262	C
1-205		445,53	446	246	B
1-206		427,89	392	267	A
1-207		425,92	390	259(dec.)	B
1-208		446,51	447	253(dec.)	B

Ex. No.	Structure	Mol Weight	MS (M+1)	mp	in vitro
1-209		482,97	447	>260	B
1-210		464,96	429	>300	A

Example 2-1:

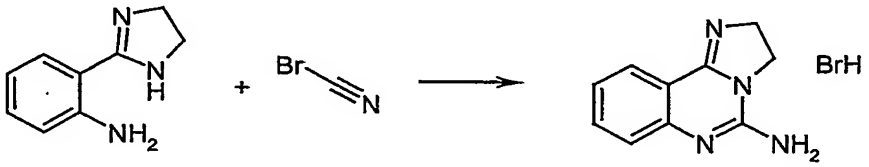
N-(2,3-Dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide

(1) 2-(4,5-Dihydro-*1H*-imidazol-2-yl)aniline



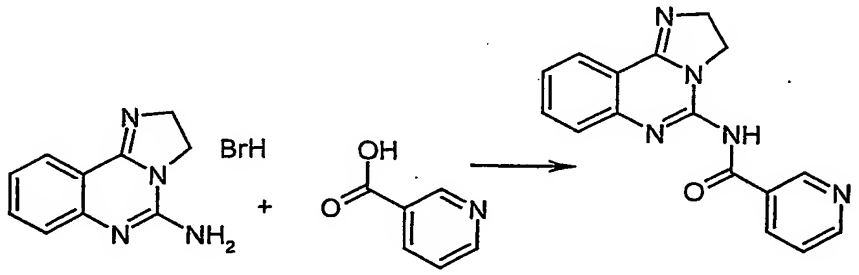
2-Aminobenzonitrile (9.00 g, 76.2 mmol) was added at 0°C to ethylenediamine (25.5 ml, 381 mmol) in small portions with stirring. After phosphorus pentasulfide (200 mg, 0.900 mmol) was added, the mixture was stirred at 100°C overnight. After cooling to 0°C, the reaction was diluted with water. The resulting white precipitate was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give 2-(4,5-dihydro-1H-imidazol-2-yl)aniline (10.0 g, 81% yield).

(2) 2,3-Dihydroimidazo[1,2-c]quinazolin-5-ylamine hydrobromide



To a suspension of 2-(4,5-dihydro-1H-imidazol-2-yl)aniline (5.00 g, 31.0 mmol) in 85% methanol (60 ml) at 0°C was added cyanogen bromide (3.61 g, 34.1 mmol) by portions. This mixture was stirred at room temperature overnight. After the mixture was concentrated under reduced pressure, the resulting precipitate was collected by filtration. This pale green solid was washed with water, methanol and diethyl ether successively, and dried under reduced pressure to give 2,3-dihydroimidazo[1,2-c]quinazolin-5-ylamine hydrobromide (4.94 g, 60% yield).

(3) *N*-(2,3-Dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



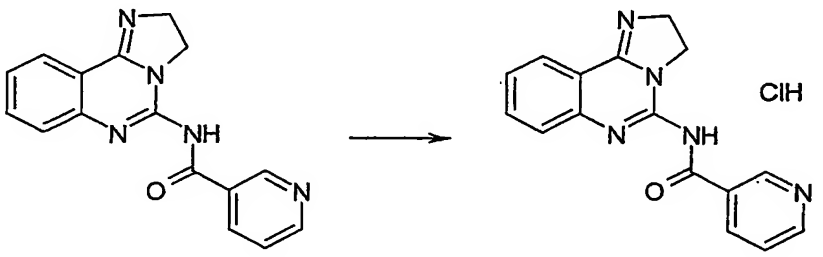
To a suspension of 2,3-dihydroimidazo[1,2-c]quinazolin-5-ylamine hydrobromide (500 mg, 1.87 mmol) and nicotinic acid (346 mg, 2.81 mmol) in *N,N*-dimethylformamide (25 ml) at room temperature was added benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (1.46 g, 2.81 mmol) followed by *N,N*-diisopropylethylamine (1.30 ml, 7.49 mmol). The mixture was heated at 80°C for 4 hours. After cooling to room temperature, the mixture was quenched with aqueous saturated $NaHCO_3$ solution. The resulting precipitate was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give N-(2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (450 mg, 83% yield).

Melting point: 238-239°C (decomposition)
Mass spectrometry: 292
In vitro PI3K-β inhibitory activity: B
In vitro PI3K-γ inhibitory activity: A

^{1}H-NMR (300 MHz, DMSO-d6): d 4.00 - 4.11 (2H, m), 4.11 - 4.21 (2H, m), 7.29 (1H, ddd, J = 3.0, 5.3, 7.9 Hz), 7.52 (1H, dd, J = 4.9, 7.9 Hz), 7.57 - 7.66 (2H, m), 7.89 (1H, d, J = 7.9 Hz), 8.42 - 8.48 (1H, m), 8.73 (1H, dd, J = 1.9, 4.9 Hz), 9.32 (1H, d, J = 1.1 Hz), 12.36 (1H, s).

Example 2-2:

N-(2,3-Dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide hydrochloride



To a suspension of *N*-(2,3-dihydroimidazo[1,2-*c*]quinazolin-5-yl)nicotinamide (150 mg, 0.515 mmol) in tetrahydrofuran (4 ml) at 0°C was added a 4N solution of hydrochloric acid in 1,4-dioxane (2 ml, 8 mmol). The mixture was stirred at room temperature for 1 h, and concentrated under reduced pressure. The resulting residue was triturated with diethyl ether. The resulting precipitate was collected by filtration, washed with ethyl ether, and dried under reduced pressure to give N-(2,3-dihydro-imidazo[1,2-c]quinazolin-5-yl)nicotinamide hydrochloride (192 mg, quantitative).

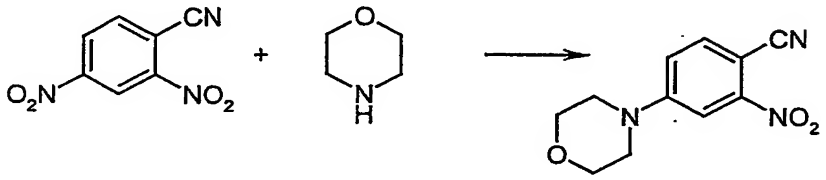
Melting point: 289°C (decomposition)
Mass spectrometry: 292
In vitro PI3K-β inhibitory activity: B
In vitro PI3K-γ inhibitory activity: A

^{1}H-NMR (300 MHz, DMSO-d6): δ 4.18 - 4.30 (2H, m), 4.54 - 4.65 (2H, m), 7.56 - 7.65 (1H, m), 7.88 (1H, dd, J = 4.9, 7.9 Hz), 7.97 - 8.10 (2H, m), 8.64 (1H, d, J = 7.9 Hz), 8.80 (1H, d, J = 7.9 Hz), 8.95 (1H, dd, J = 1.5, 5.3 Hz), 9.43 (1H, d, J = 1.1 Hz), 12.7 - 13.3 (1H, br).

Example 2-3:

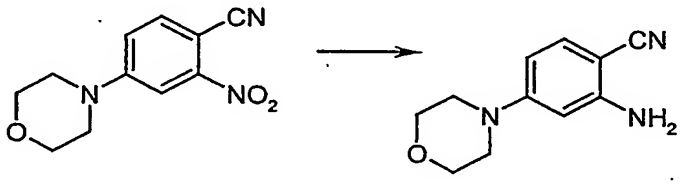
6-(Acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

(1) 4-(Morpholin-4-yl)-2-nitrobenzonitrile



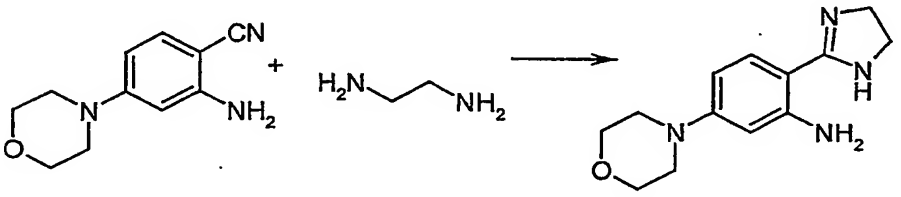
A mixture of 2,4-dinitrobenzonitrile 4.20g (21.75mmol) and morpholine 5.7mL (66.0mmol) in N,N-dimethyformamide 20mL was stirred at room temperature for 20 hours. The reaction mixture was poured into water. The precipitate was collected and washed with water to give the title compound 4.20g as orange solid. Yield 74.5%.

(2) 2-Amino-4-(morpholin-4-yl)benzonitrile



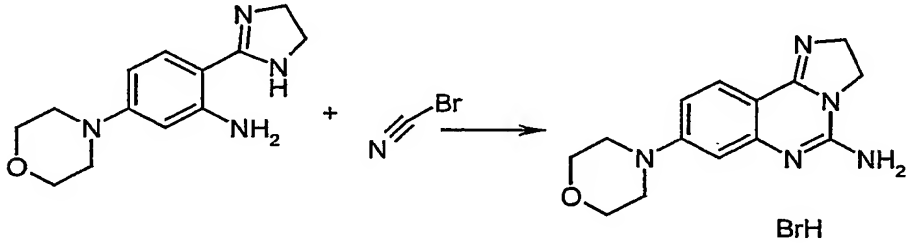
To a cooled mixture of tin(II) chloride dihydrate 12.8g (56.7mmol) in conc. HCl 40mL with ice bath was added 4-(morpholin-4-yl)-2-nitrobenzonitrile 4.20 g (16.09mmol) and stirred at room temperature for 2 hours. The reaction mixture was poured into diluted NaOH solution and extracted into ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated. The crude product was washed with diethyl ether to give the title compound 3.13g as off-white solid. Yield 95.0%.

(3) [2-(4,5-dihydro-1H-imidazol-2-yl)-5-(morpholin-4-yl)phenyl]amine



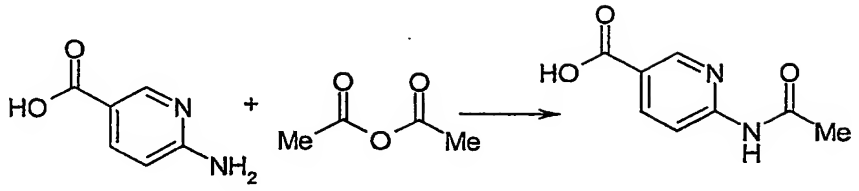
To a solution of 2-amino-4-(morpholin-4-yl)benzonitrile 3.65g (18.0 mmol) in ethylenediamine 20mL was added phosphorus pentasulfide 4.00mg (0.018 mmol) and stirred at 140°C for 16 hours. After cooling to room temperature, the solvent was evaporated. The residue was washed with water and diethyl ether to give the title compound 3.70g as off-white solid. Yield 83.5%.

(4) 8-(Morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine hydrobromide



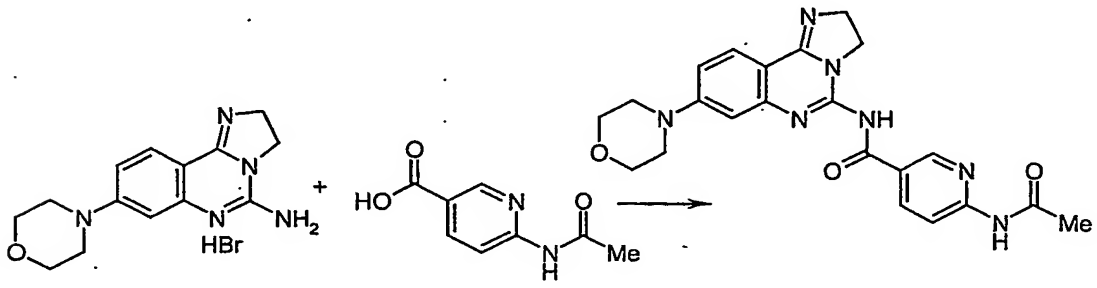
To a suspension of [2-(4,5-dihydro-1H-imidazol-2-yl)-5-(morpholin-4-yl)phenyl]amine 3.60g (14.6mmol) in 2-propanol 20mL was added cyanogen bromide 2.32g (21.9mmol) portionwise at 0°C and stirred at 100°C for 2 hours. After cooling to room temperature, the precipitate was collected and washed with diethyl ether to give the title compound 1.20g as yellow solid. Yield 77.5%.

(5) 6-(Acetamido)nicotinic acid



A mixture of 6-aminonicotinic acid 5.00g (36.5mmol) and acetic anhydride 3.80mL (40.2mmol) in pyridine 30mL was stirred at 140°C for 24 hours. To the reaction mixture was added ethyl acetate and acidified with diluted HCl solution to pH 2. The organic layer was washed with water and brine, dried over $MgSO_4$, filtrated and the solvent was evaporated. The residue was washed with diisopropyl ether to give the title compound 1.70g as off-white solid. Yield 26%.

(6) 6-(Acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide



To a mixture of 8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine hydrobromide 105.7mg (0.30mmol), 6-(acetamido)nicotinic acid 81.1mg (0.45mmol) and N,N-diisopropylethylamine 0.26mL (1.50mmol) in N,N-dimethylformamide 2 mL was added PyBOP((1H-1,2,3-benzotriazol-1-yloxy)(tripyrrolidin-1-yl)-phosphonium hexafluorophosphate) 234.2mg (0.45mmol) and stirred at 90°C for 16 hours. After cooling to room temperature, saturated $NaHCO_3$ solution was added. The precipitate was collected and washed with water, methanol, and diethyl ether to give the title compound 41.1mg as yellow solid. Yield 31.6%.

Melting point: 228°C

Mass spectrometry: 434

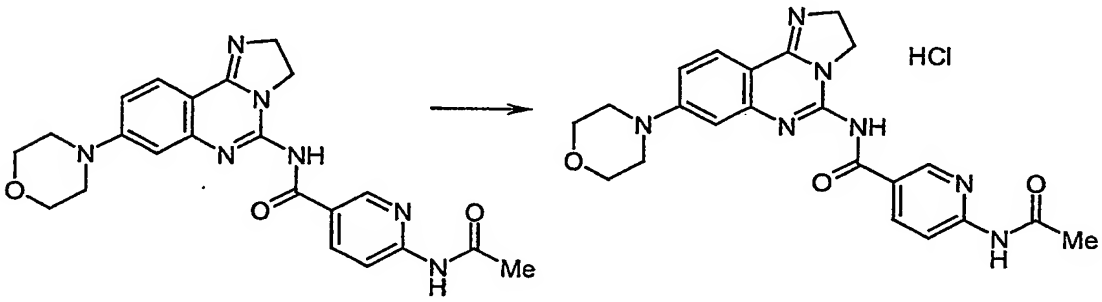
In vitro PI3K-β inhibitory activity: C

In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, DMSO-d_6) δ: 3.22-3.30 (m 4H), 3.74 (s 3H), 3.86 (m 2H), 3.97 (m 2H), 6.77 (br s 1H), 7.60 (m 1H), 8.07 (m 1H), 8.32 (m 1H), 8.95 (br s 1H), 10.60 (s 1H)

Example 2-4:

6-(Acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride



To a mixture of 6-(acetamido)-N-[8-(morpholin-4-yl)-2,3-dihydroimidazo[1,2-c]-quinazolin-5-yl]nicotinamide (Example 2-3) 20.0mg (0.046mmol) in 1,4-dioxane 1.5mL was added 4N HCl in 1,4-dioxane 0.5mL and stirred at room temperature for 40 minutes. The precipitate was collected and washed with diethyl ether to give the title compound 17.0mg as yellow solid. Yield 78%.

Melting point: 237°C

Mass spectrometry: 434

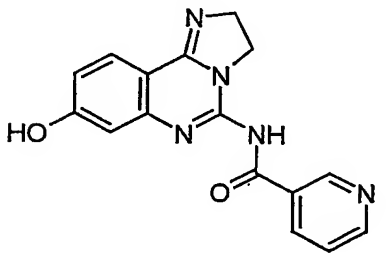
In vitro PI3K-β inhibitory activity: B

In vitro PI3K-γ inhibitory activity: A

H-NMR (500MHz, DMSO-d_6) δ: 3.41-3.76 (m 7H), 3.86 (m 2H), 4.10 (m 2H), 7.20 (m 1H), 7.39 (m 1H), 8.19 (m 1H), 8.45 (m 1H), 9.09 (br s 1H), 10.86 (s 1H)

Example 2-5:

N-(8-Hydroxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



A suspension of N-(8-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (example 2-22) 3.50g (10.9mmol) and sodium sulfide 4.25g (54.5mmol) in 1-methyl-2-pyrrolidinone 10mL was heated to 160°C for 4 hours (LC-MS indicated complete consumption of the starting matrial). The mixture was cooled to room temperature and volatile sideproducts were evaporated. The mixture was partitioned between chloroform and 0.5N NaOH solution. The aqueous layer was neutralized and the formed precipitate was collected to give the title compound 2.34g as off-white solid. Yield 69.9%.

Melting point: 289°C

Mass spectrometry: 308

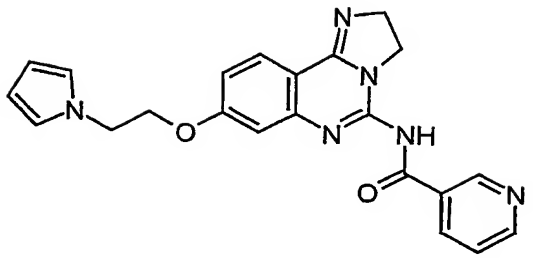
In vitro PI3K-β inhibitory activity: C

In vitro PI3K-γ inhibitory activity: B

H-NMR (500MHz, DMSO-d_6) δ: 4.01(m 2H), 4.15(m 2H), 6.75(dd 1H J=8Hz, 2Hz), 6.91(s 1H), 7.52(dd 1H J=8Hz, 5Hz), 7.75(d 1H J=8Hz), 8.44(d 1H J=8Hz), 8.73(dd 1H J=5Hz, 2Hz), 9.31(s 1H), 10.61(br s 1H), 12.24(br s 1H)

Example 2-6:

N-{8-[2-(1-pyrrolyl)ethoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide



The suspension of N-(8-Hydroxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (example 2-1) 70.0mg (0.23mmol), N-(2-bromoethyl)pyrrole 47.6mg (0.27mmol) and potassium carbonate 126mg (0.91mmol) in N,N-dimethylformamide 5mL was heated in a sealed tube to 120°C for 3 hours. The reaction mixture was concentrated and partitioned between dichloromethane and water. The organic layer was washed with 0.1N NaOH solution and brine, dried over Na_2SO_4 and the solvent was evaporated to give the title compound 49.0mg as off-white solid. Yield 54%.

Melting point: 209°C

Mass spectrometry: 401

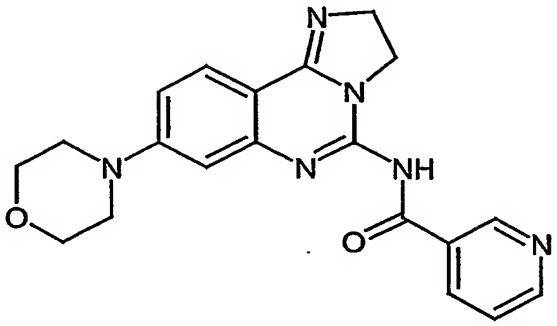
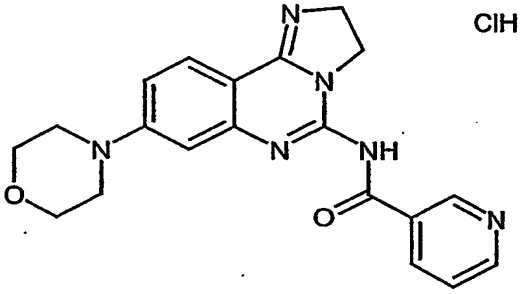
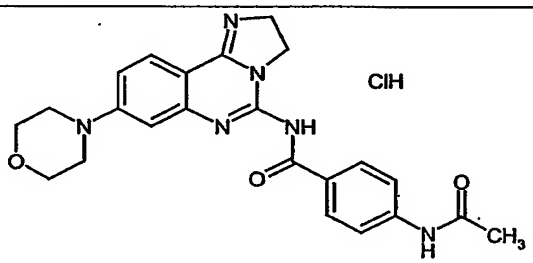
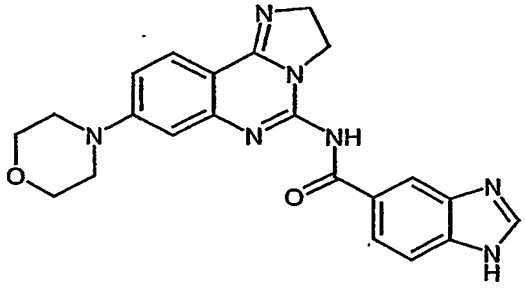
In vitro PI3K-β inhibitory activity: B

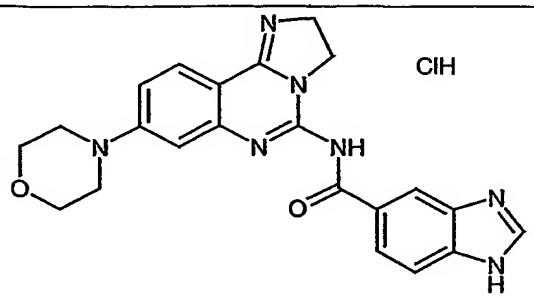
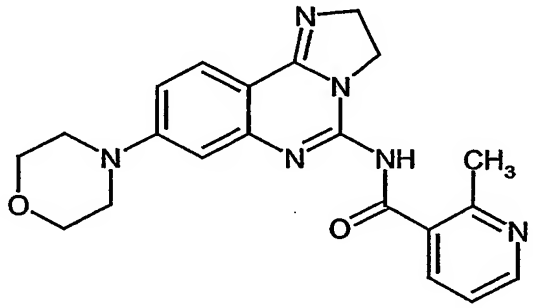
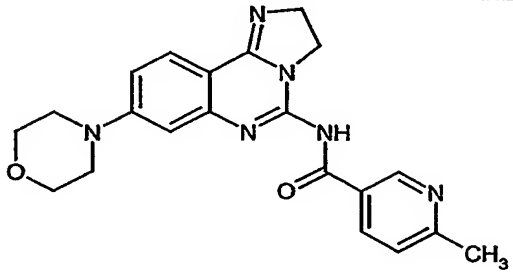
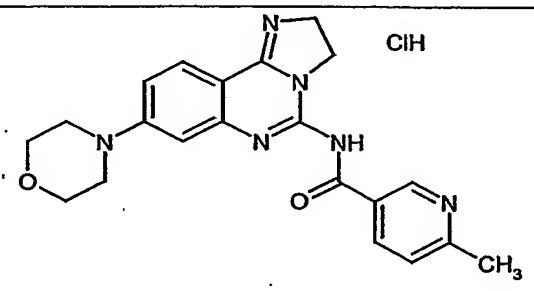
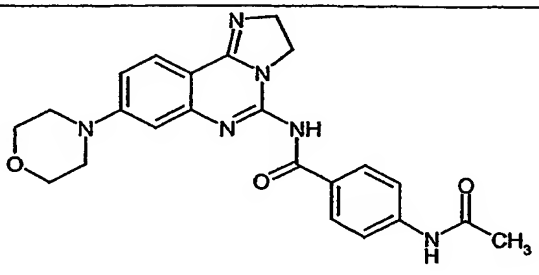
In vitro PI3K-γ inhibitory activity: B

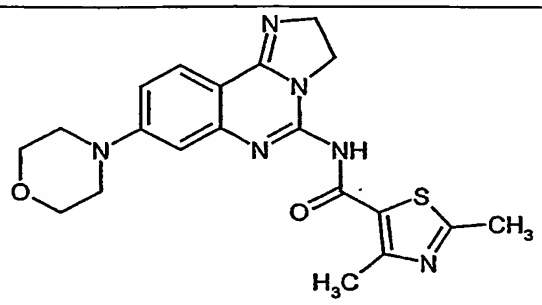
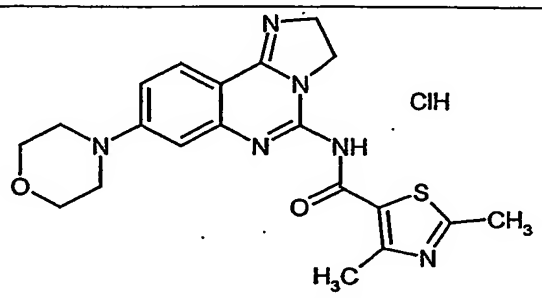
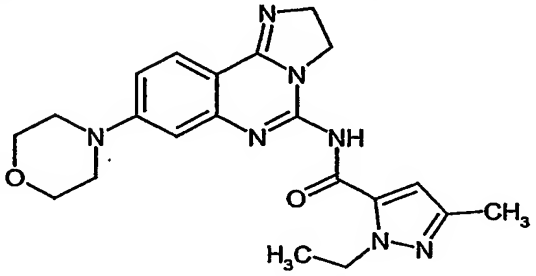
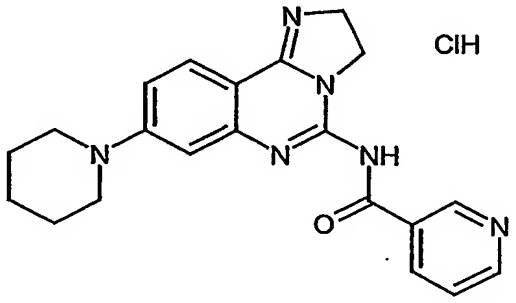
H-NMR (500MHz, DMSO-d_6) δ: 4.00(m 2H), 4.12(m 2H), 4.30(s 4H), 6.00(m 2H), 6.84(m 2H), 6.85(dd 1H J=6Hz, 2Hz), 7.27(d 1H J=2Hz), 7.52(dd 1H J=6Hz), 7.76(d 1H J=8Hz), 8.44(dd 1H J=8Hz, 2Hz), 8.72(dd 1H J=5Hz, 2Hz), 9.31(s 1H), 12.32(s 1H)

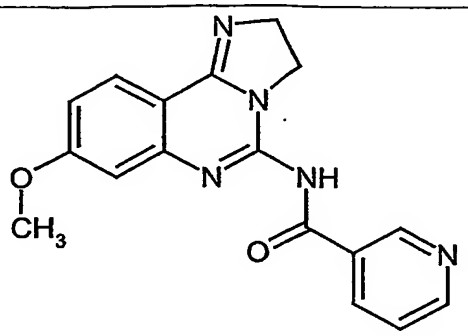
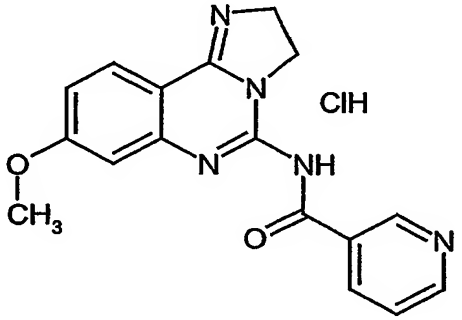
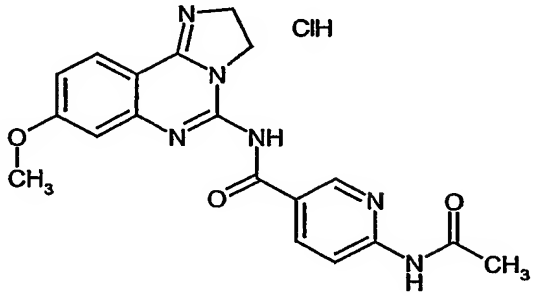
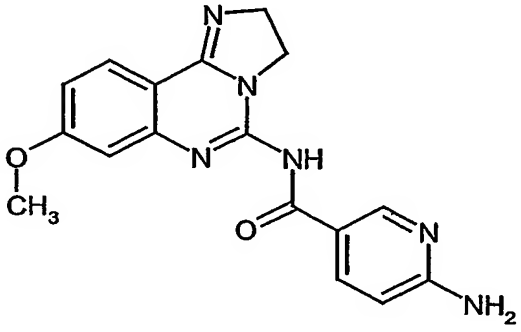
In a similar method according to the Example 2-1 to 2-6 above, the compounds in Example 2-7 to 2-368 were synthesized.

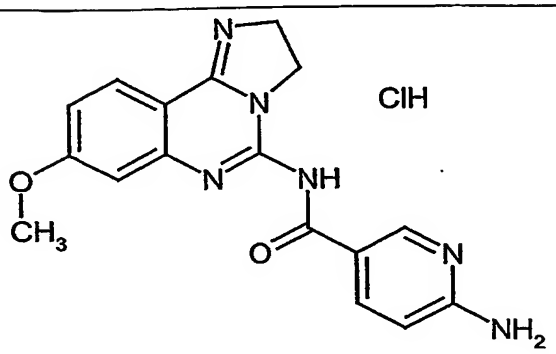
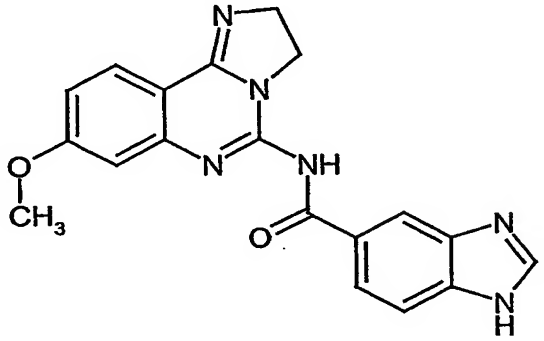
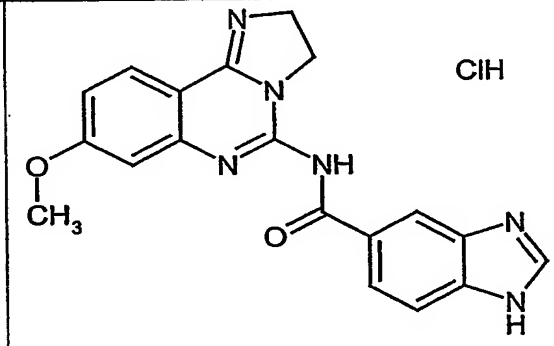
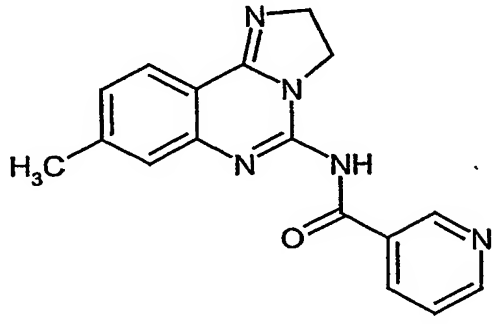
Table 2

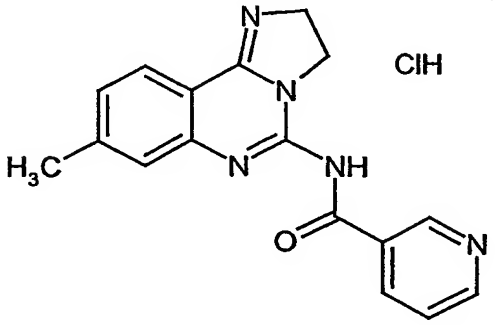
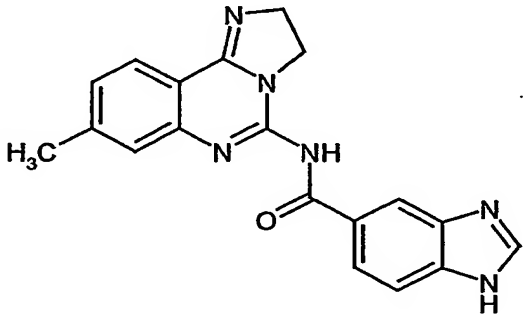
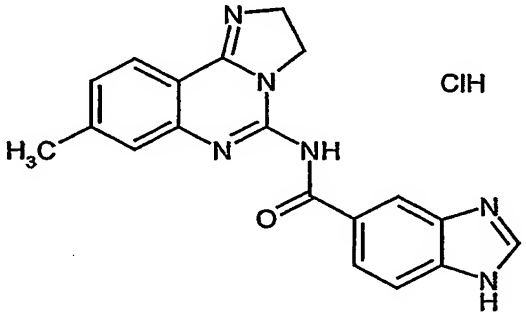
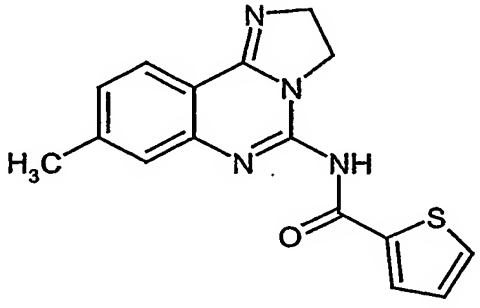
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-7		376,42	377	243	B
2-8		412,88	377	283	A
2-9		468,95	433	249	B
2-10		415,46	416	250(dec.)	B

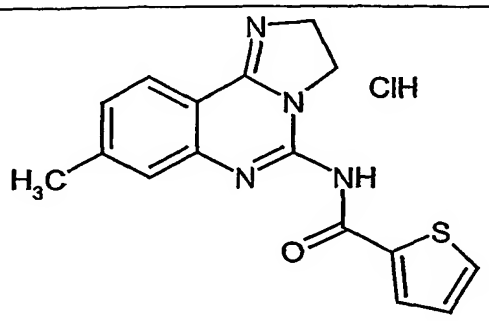
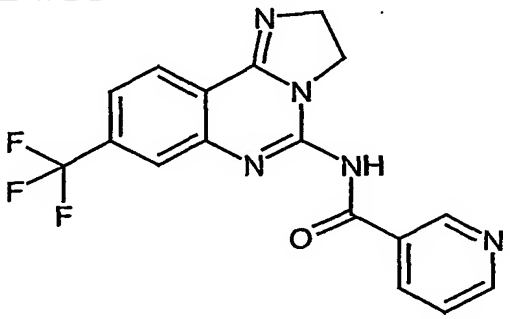
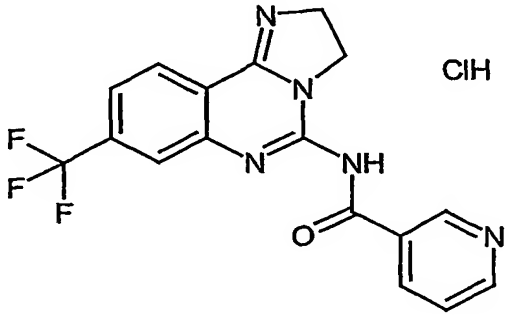
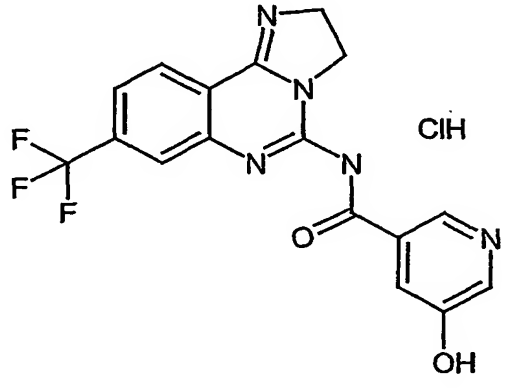
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-11		451,92	416	294(dec.)	A
2-12		390,45	391	199(dec.)	B
2-13		390,45	391	209	A
2-14		426,91	391	267(dec.)	A
2-15		432,49	433	227	B

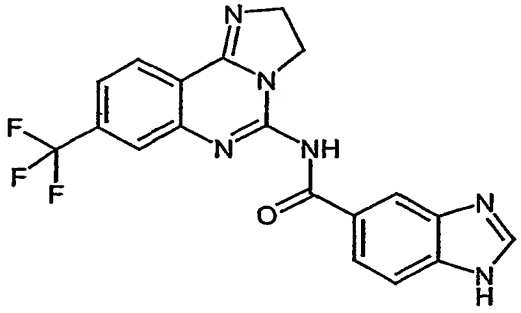
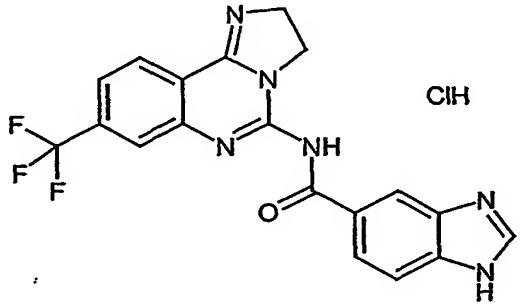
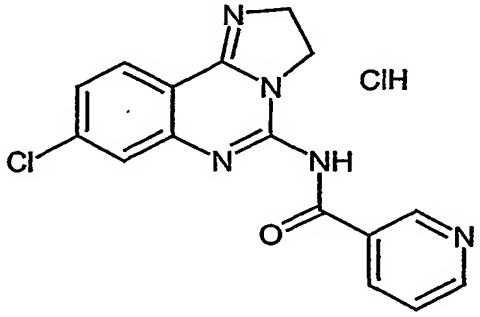
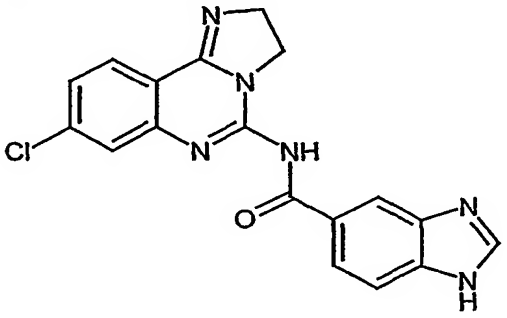
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-16		410,50	411	233(dec.)	B
2-17		446,96	411	255(dec.)	A
2-18		407,48	408	232	B
2-19		410,91	376	>300	B

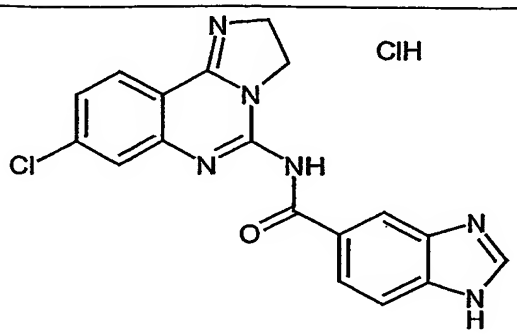
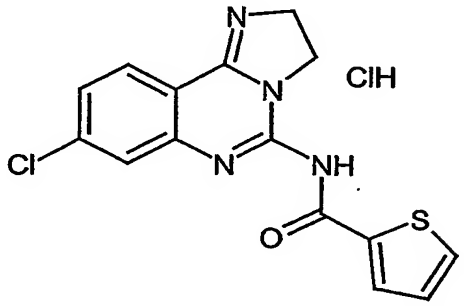
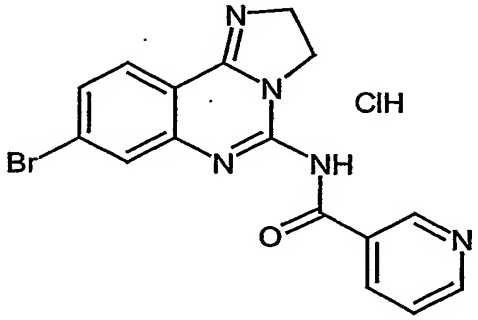
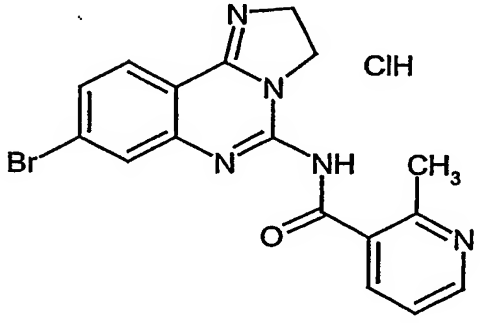
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-20		321,34	322	281(dec.)	B
2-21		357,80	322	292(dec.)	B
2-22		414,85	379	198-205(dec.)	B
2-23		336,36	337	279-282	A

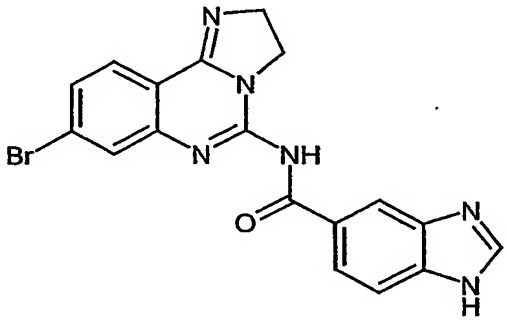
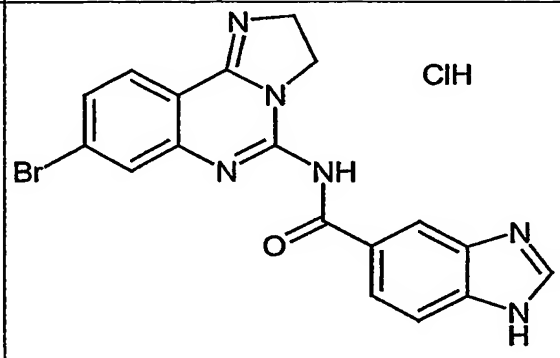
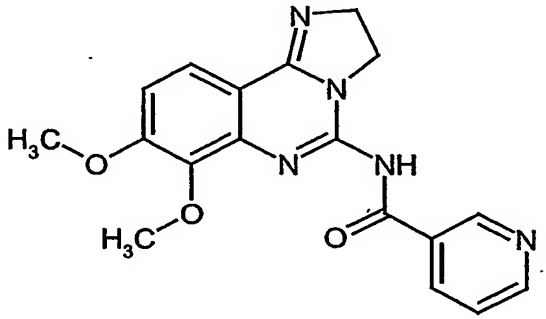
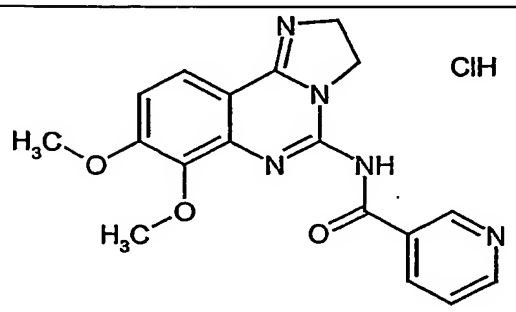
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-24		372,82	337	273(dec.)	A
2-25		360,38	361	186	A
2-26		396,84	361	233	A
2-27		305,34	306	207	A

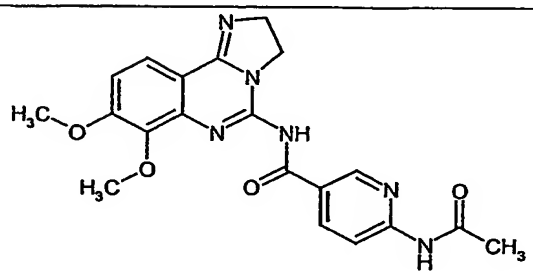
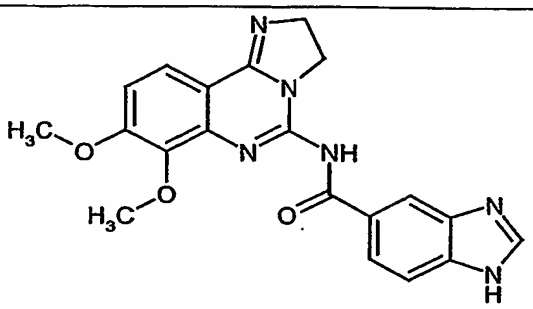
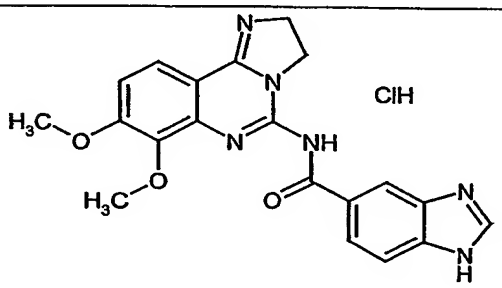
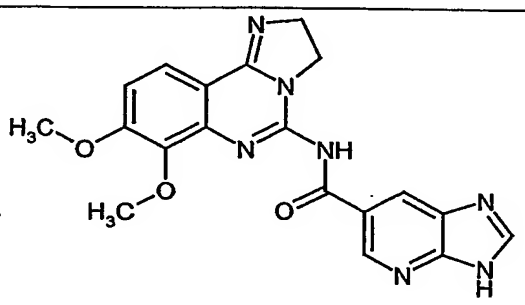
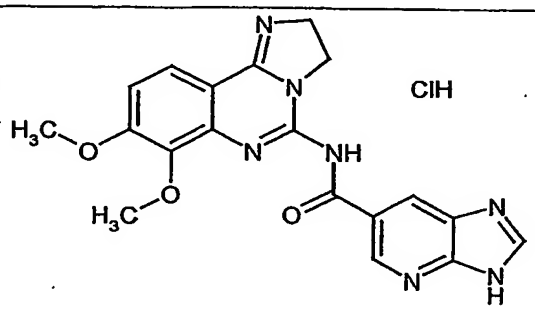
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-28		341,80	306	315	A
2-29		344,38	345	190	A
2-30		380,84	345	295	B
2-31		310,38	311	182	B

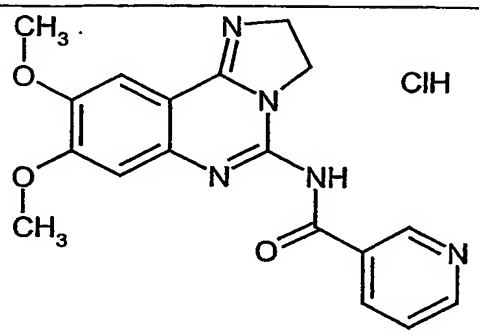
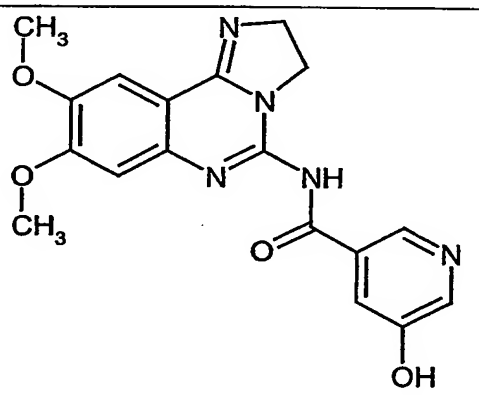
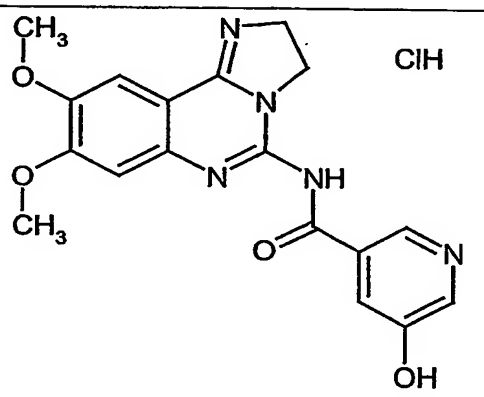
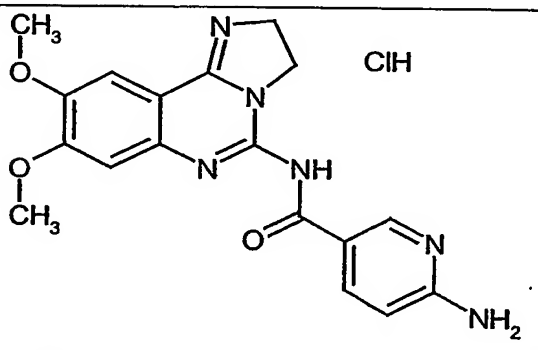
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-32		346,84	311	276	B
2-33		359,31	360	229	B
2-34		395,77	360	275	A
2-35		411,77	375	237(dec.)	A

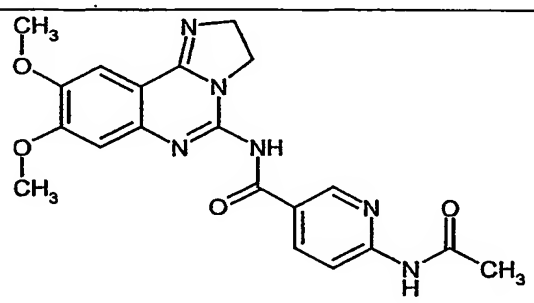
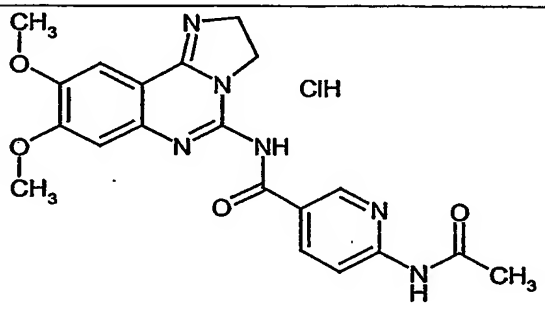
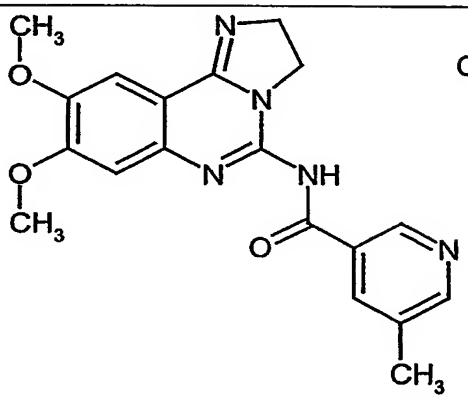
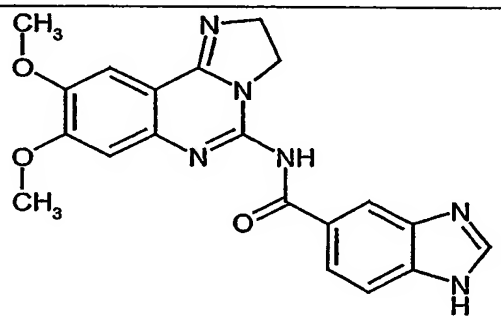
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-36		398,35	399	>300	B
2-37		434,81	399	288	A
2-38		362,22	327	308	B
2-39		364,80	366	288	A

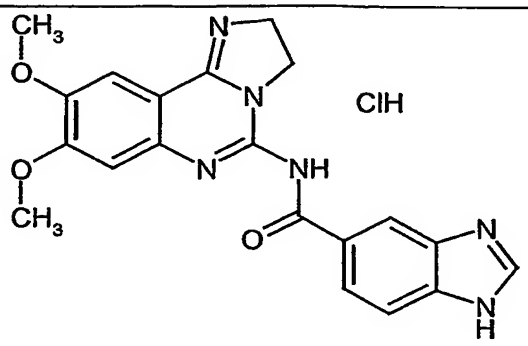
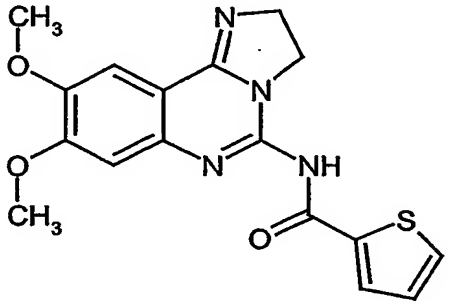
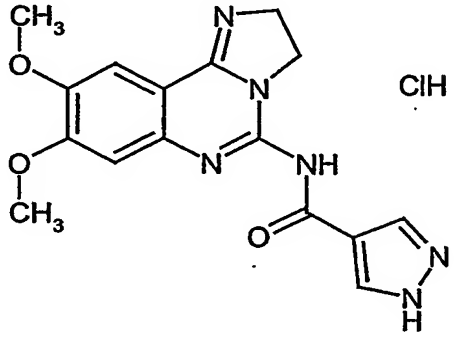
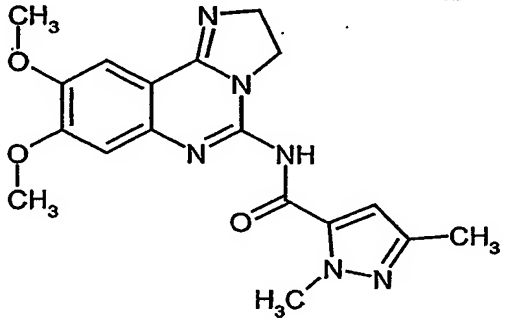
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-40		401,26	366	.270	A
2-41		367,26	332	328	B
2-42		406,67	372, 370	243	A
2-43		420,70	386, 384	252(dec.)	B

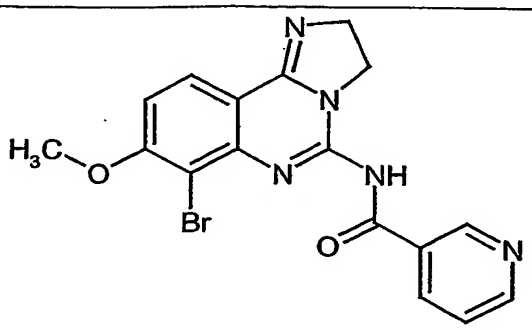
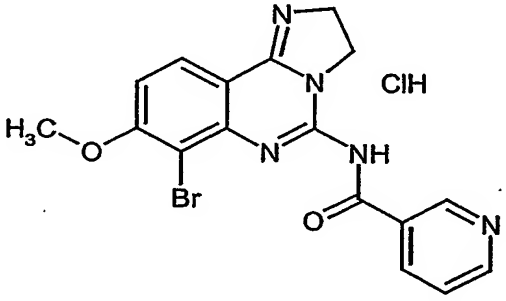
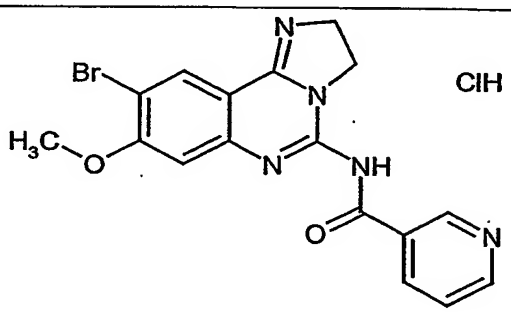
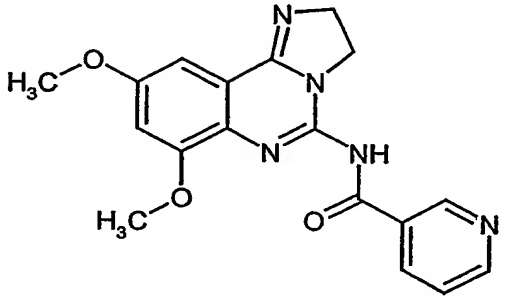
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-44		409,25	411, 409	262	B
2-45		445,71	411, 409	278	A
2-46		351,37	352	259-260	A
2-47		387,83	352	257-257	A

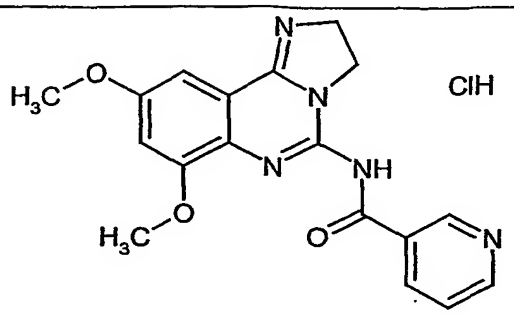
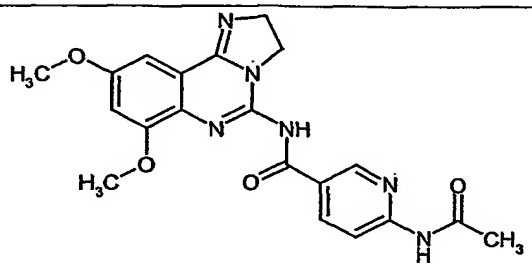
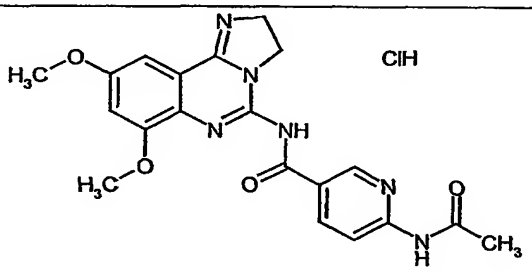
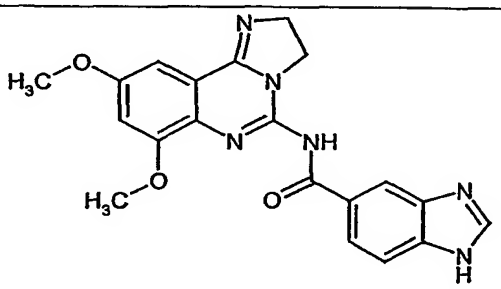
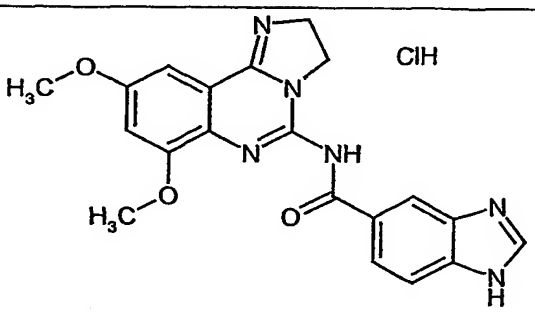
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-48		408,42	409	306-307	A
2-49		390,40	391	289(dec.)	A
2-50		426,87	391	278(dec.)	A
2-51		391,39	392	233(dec.)	A
2-52		427,85	392	210(dec.)	A

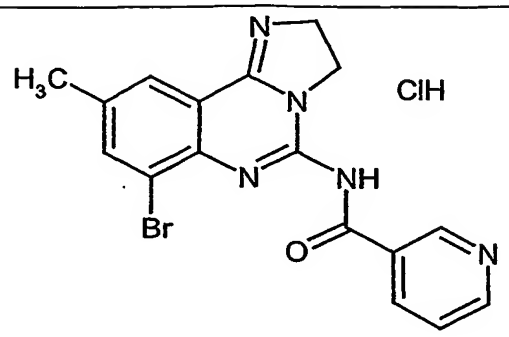
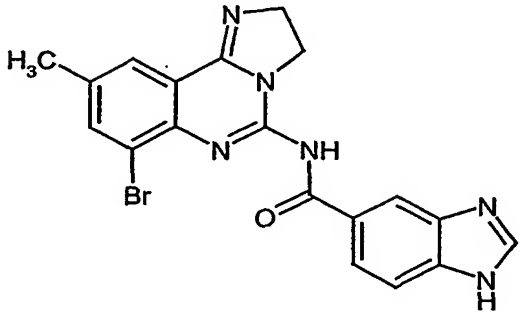
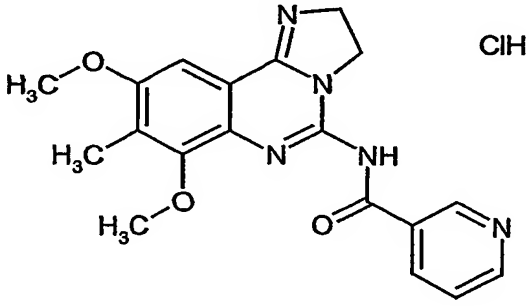
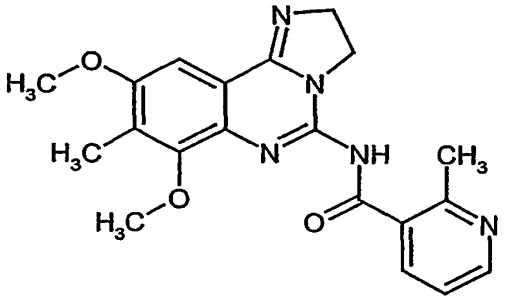
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-53		387,83	352	246	B
2-54		367,37	367	287(dec.)	A
2-55		403,83	367	260(dec.)	A
2-56		402,84	367	256	B

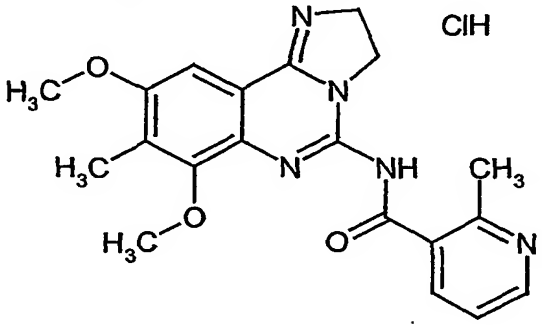
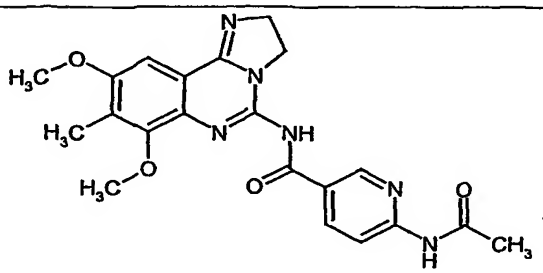
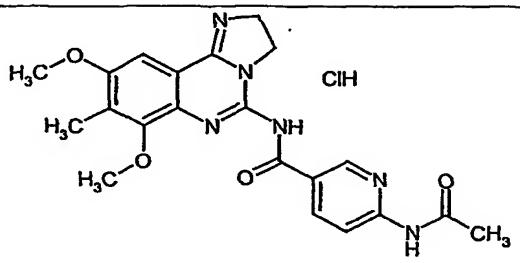
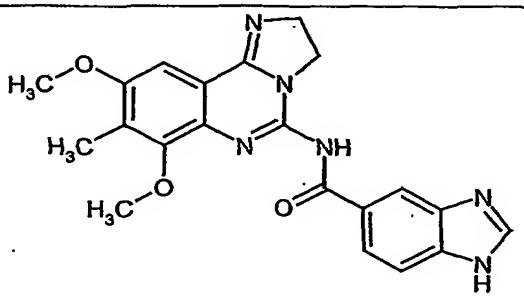
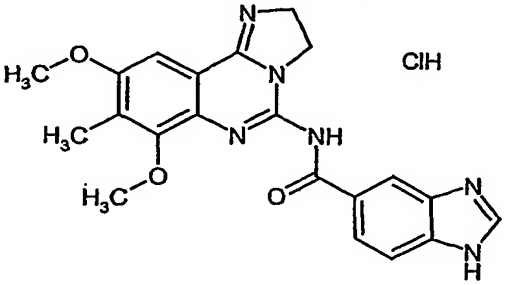
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-57		408,42	409	224	B
2-58		444,88	409	279	B
2-59		401,86	366	257(dec.)	B
2-60		390,40	391	246	A

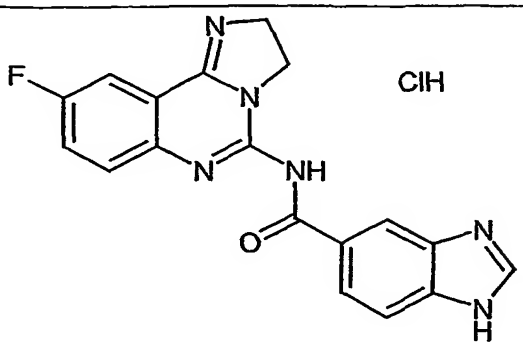
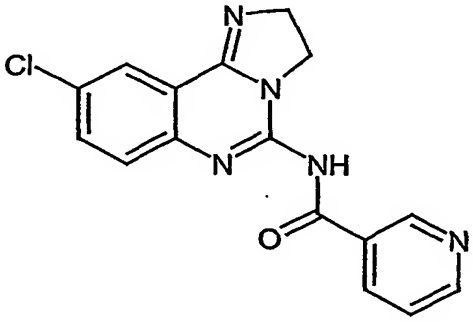
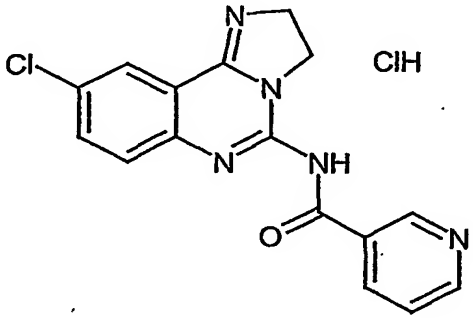
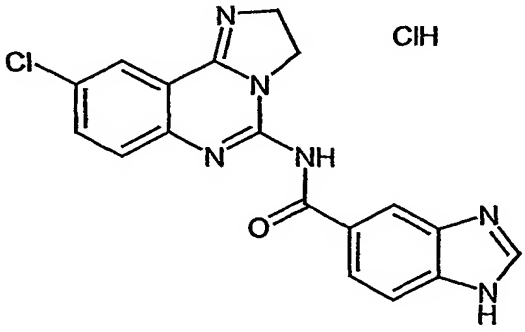
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-61		426,87	391	276	A
2-62		356,41	357	248	B
2-63		376,81	340	270(dec.)	B
2-64		368,40	368	236-237	B

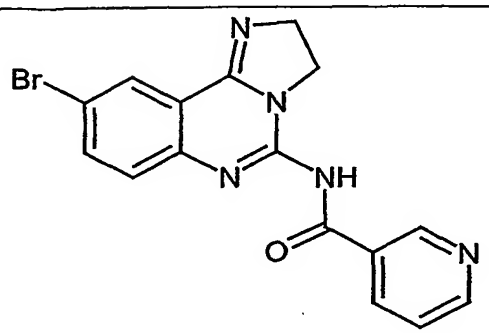
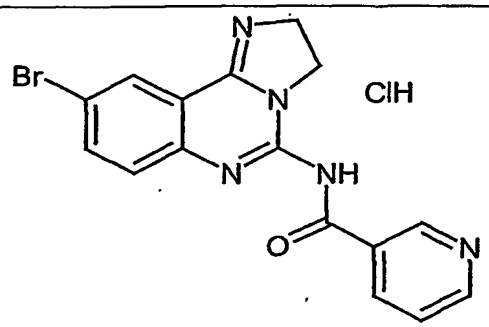
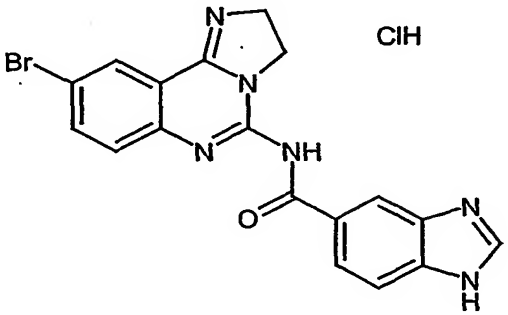
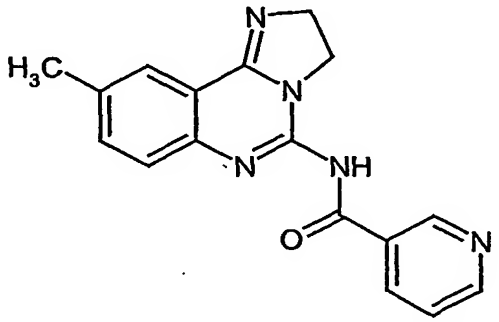
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-65		400,24	402, 400	264	A
2-66		436,70	402, 400	298	A
2-67		436,70	402, 400	289(dec.)	B
2-68		351,37	352	228(dec.)	A

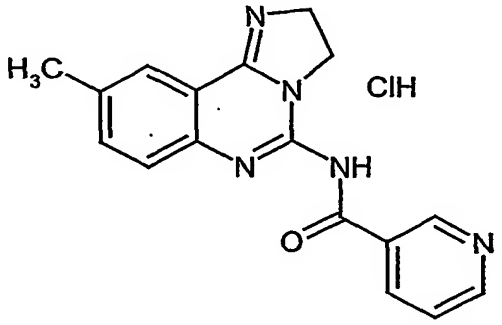
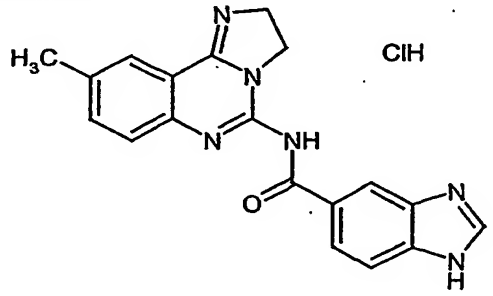
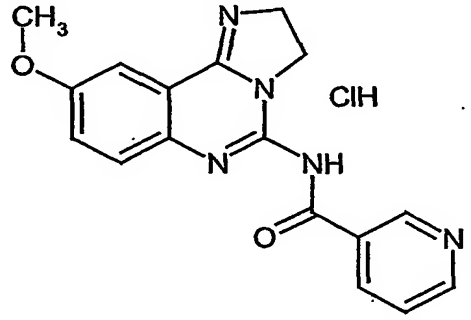
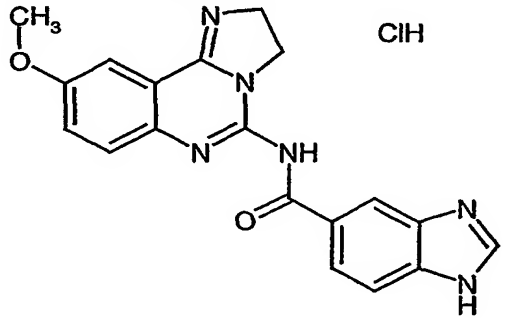
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-69		387,83	352	275(dec.)	B
2-70		408,42	408	286(dec.)	B
2-71		444,88	408	270(dec.)	B
2-72		390,40	391	210(dec.)	A
2-73		426,87	391	289(dec.)	A

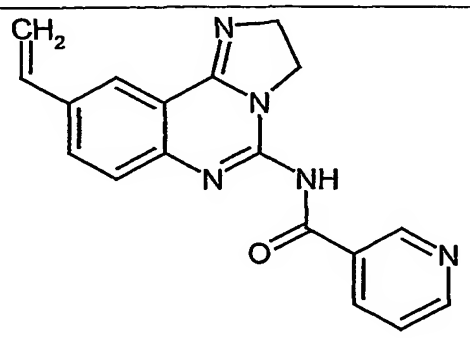
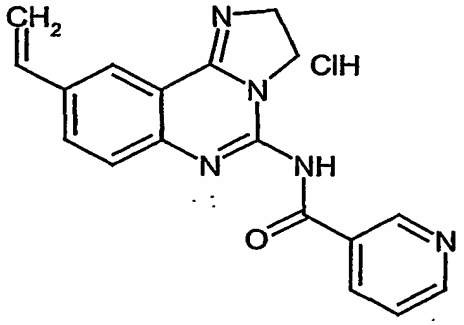
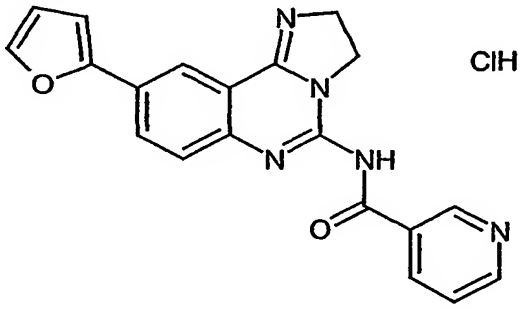
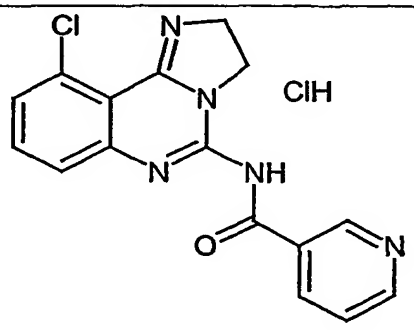
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-74		420,70	386, 384	220	A
2-75		423,28	425, 423	>290	B
2-76		401,86	366	235(dec.)	B
2-77		379,42	379	210(dec.)	A

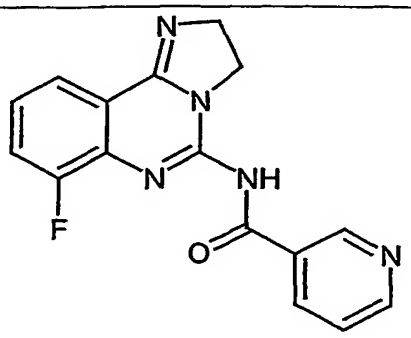
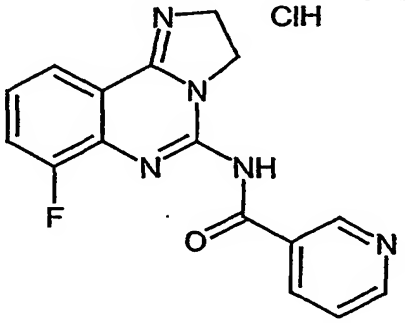
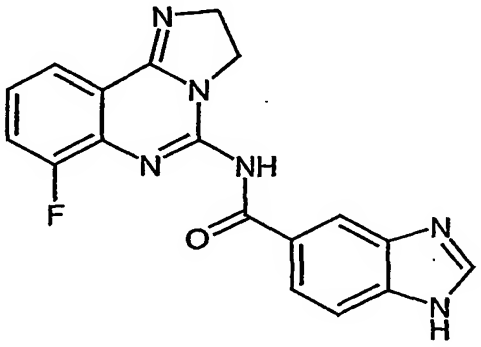
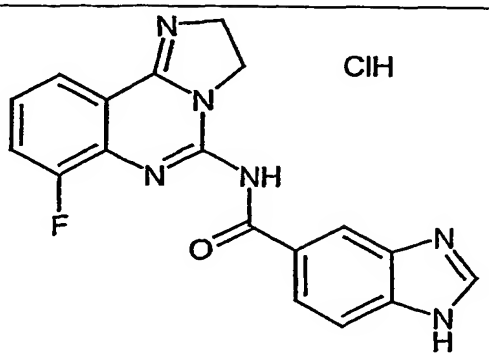
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-78		415,88	379	230(dec.)	A
2-79		422,45	422	> 310	B
2-80		458,91	422	305(dec.)	A
2-81		404,43	405	202	B
2-82		440,89	405	280(dec.)	B

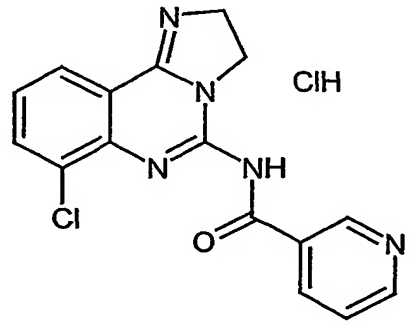
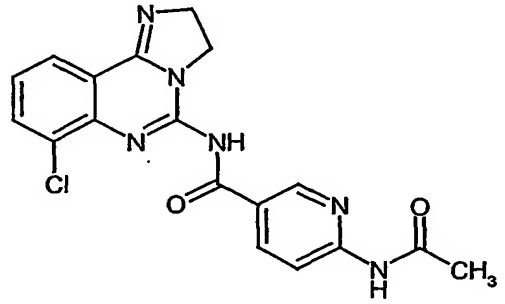
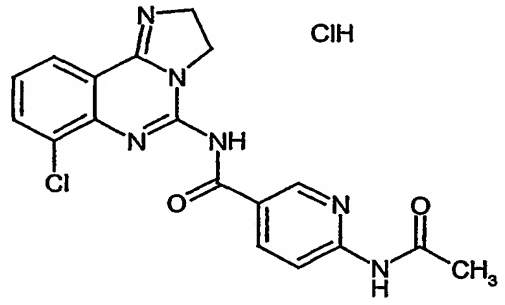
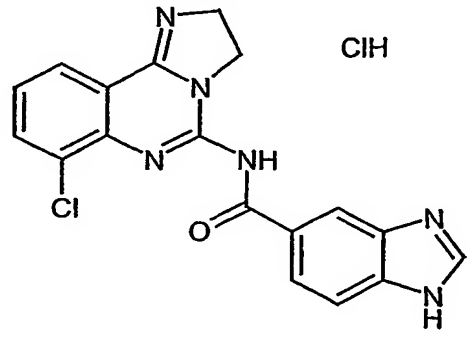
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-83		384,80	349	>300	B
2-84		325,76	326	210	B
2-85		362,22	327	309	B
2-86		401,26	366	305(dec.)	B

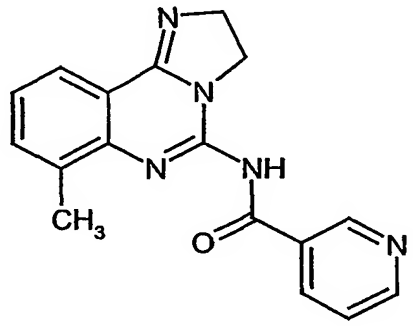
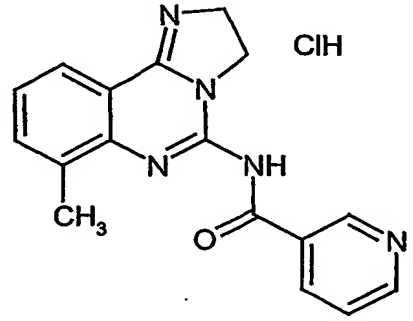
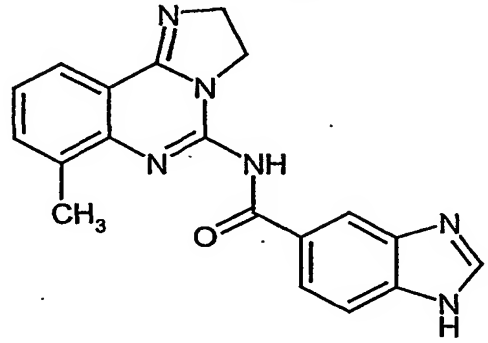
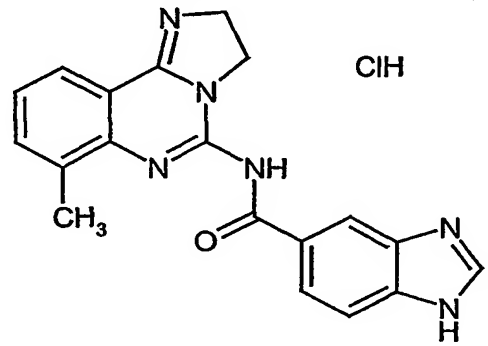
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-87		370,21	372	228	B
2-88		406,67	372, 370	316	B
2-89		445,71	411, 409	288	B
2-90		305,34	306	210	A

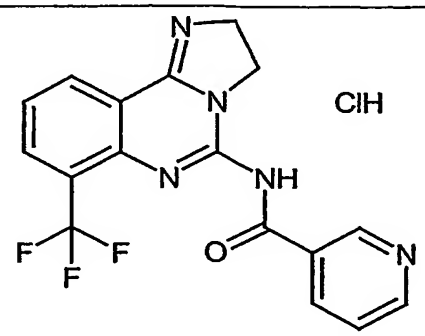
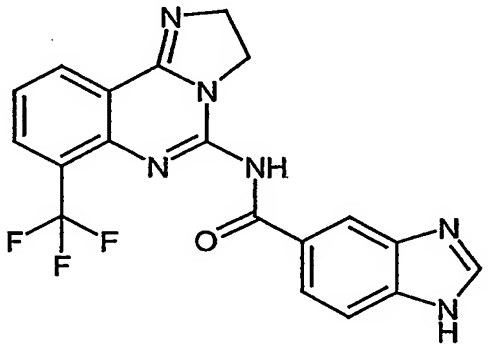
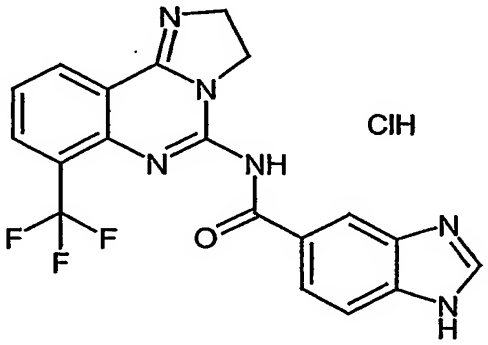
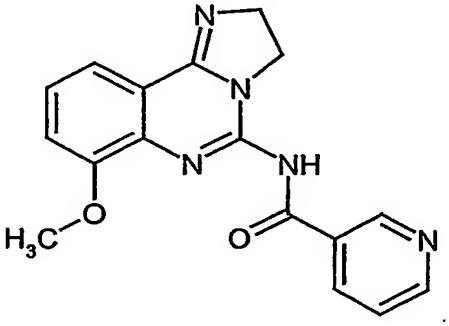
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-91		341,80	306	>290	B
2-92		380,84	345	>290	A
2-93		357,80	322	>300	B
2-94		396,84	361	288	A

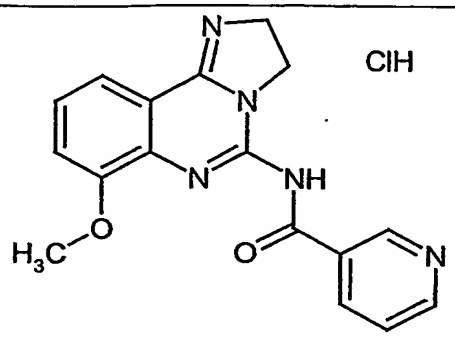
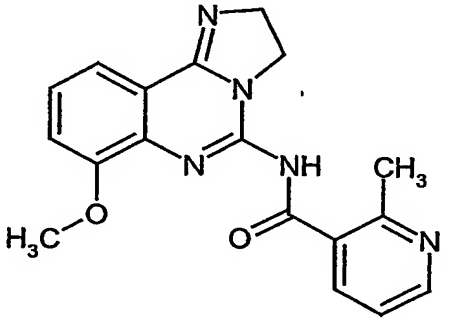
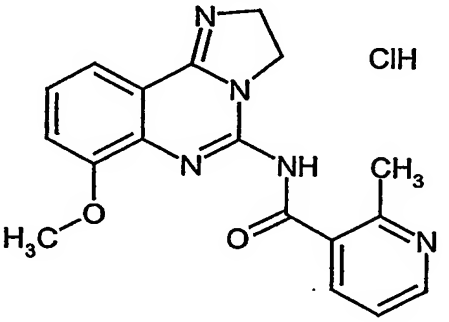
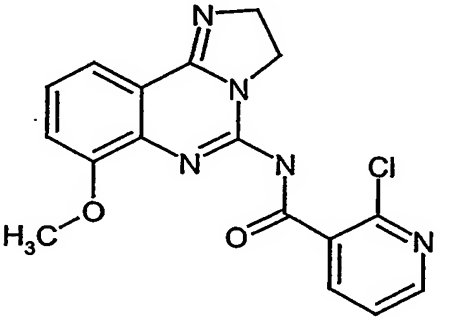
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-95		317,35	318	196-198	B
2-96		353,81	318	275-277	B
2-97		393,84	358	298-299	B
2-98		362,22	327	249	B

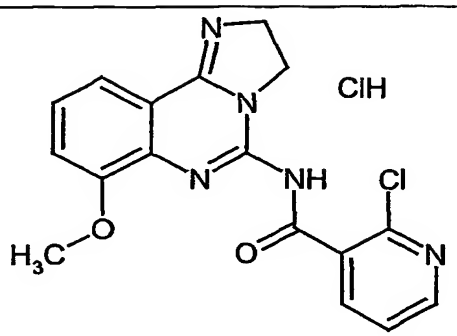
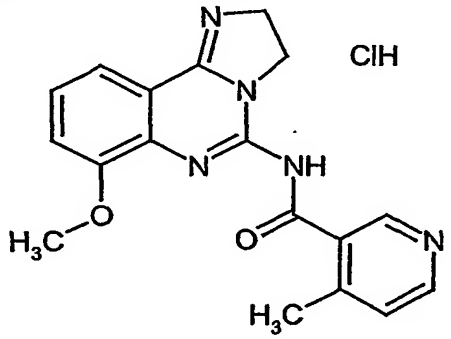
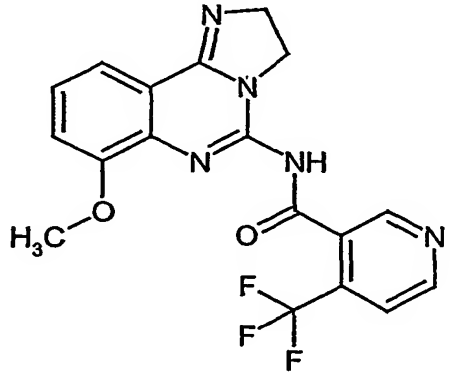
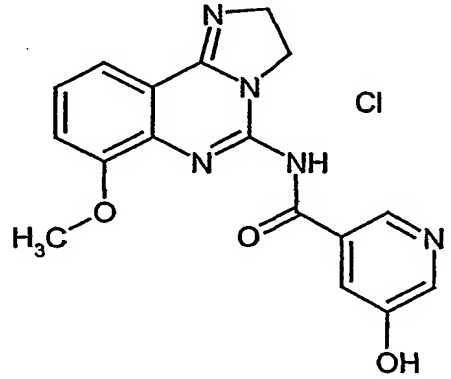
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-99		309,31	310	243	B
2-100		345,77	310	288	A
2-101		348,34	349	>300	A
2-102		384,80	349	>300	A

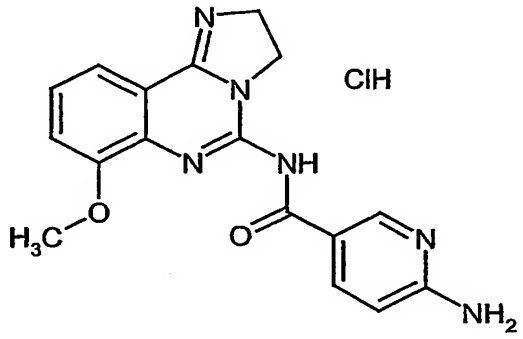
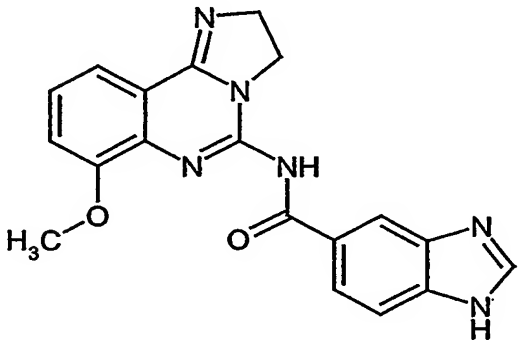
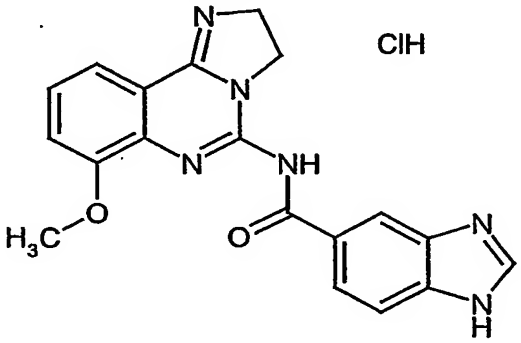
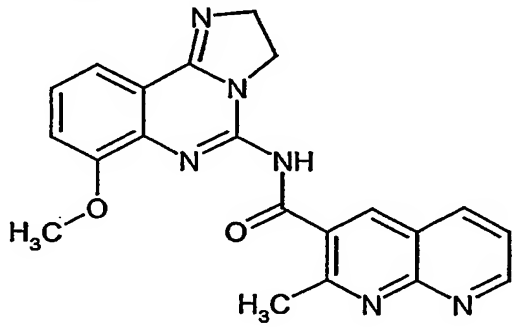
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-103		362,22	326	>280	B
2-104		382,81	383	> 280	B
2-105		419,27	383	> 280	A
2-106		401,26	365	> 280	B

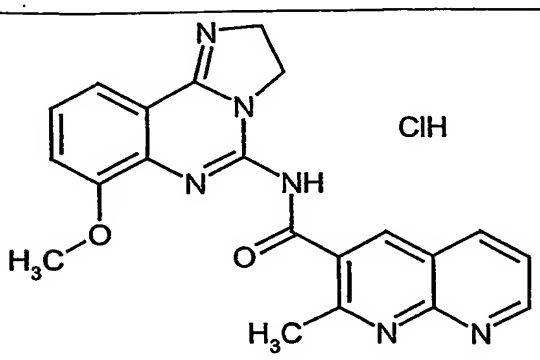
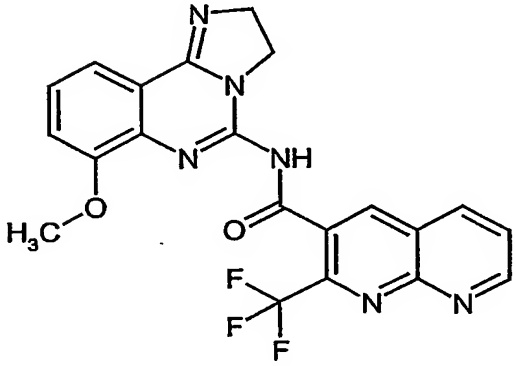
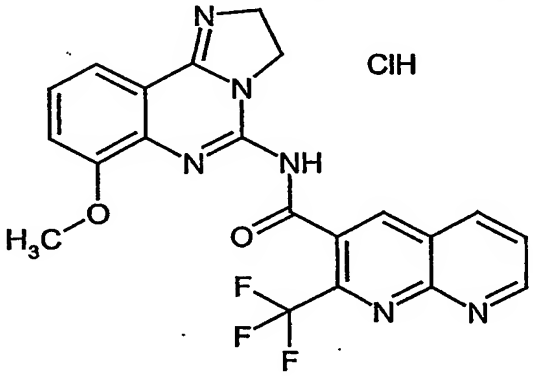
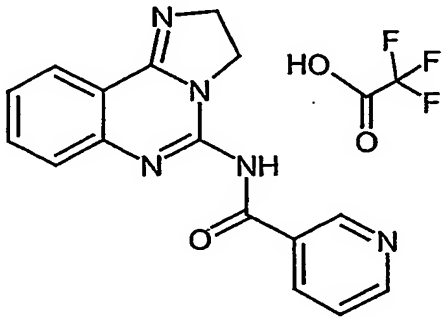
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-107		305,34	306	244	B
2-108		341,80	306	>290	B
2-109		344,38	345	>290	A
2-110		380,84	345	>290	A

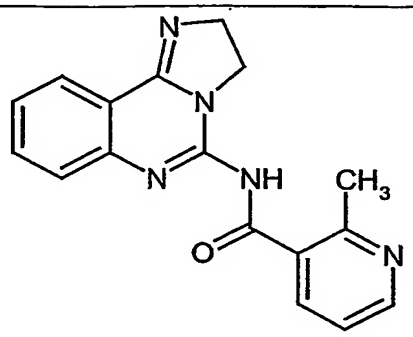
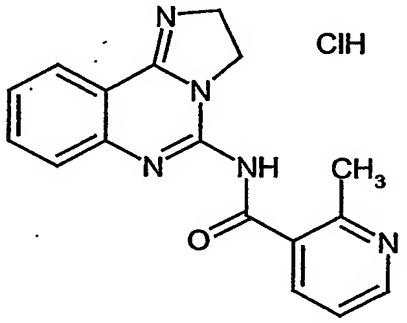
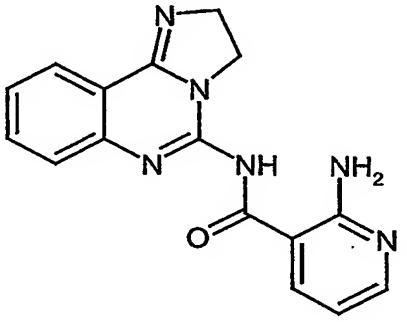
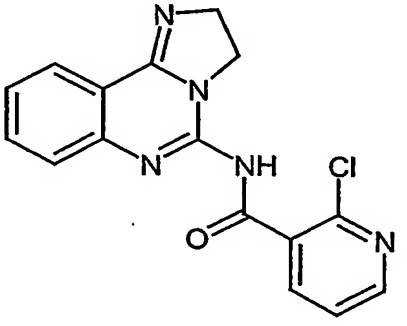
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-111		395,77	360	263	A
2-112		398,35	399	286	A
2-113		434,81	399	270	A
2-114		321,34	322	110	A

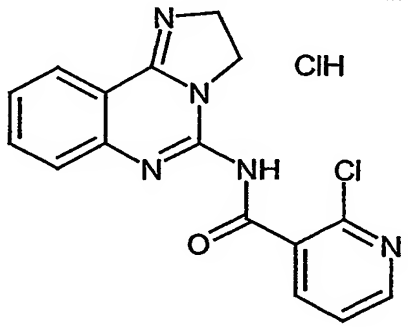
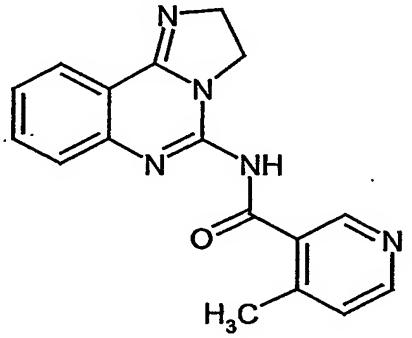
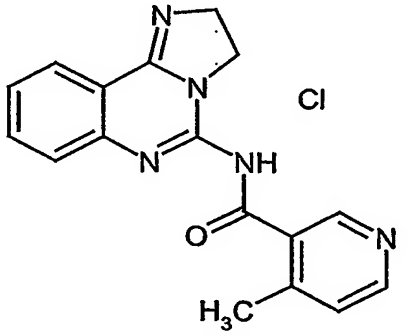
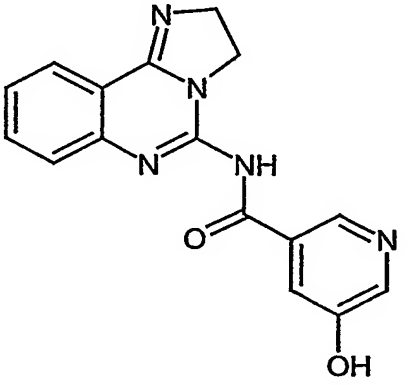
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-115		357,80	322	237(dec.)	A
2-116		335,37	335	204-205	B
2-117		371,83	335	251(dec.)	A
2-118		355,79	355	185(dec)	A

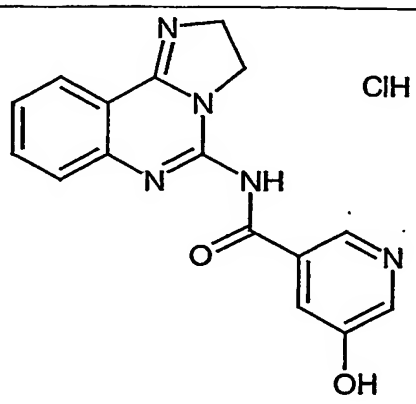
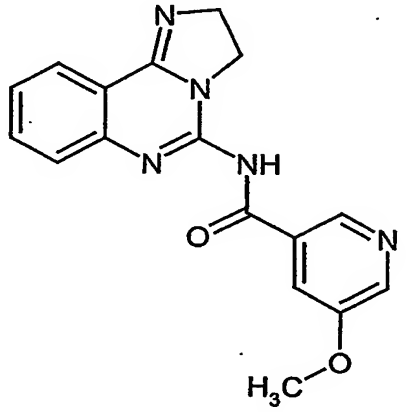
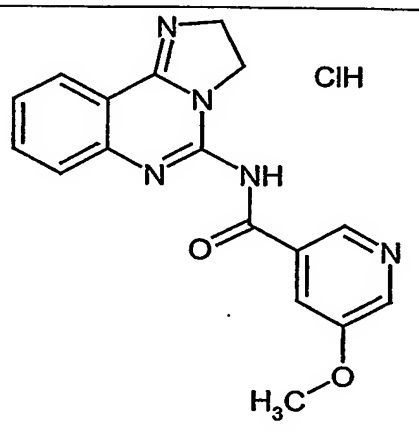
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-119		392,25	355	266(dec.)	A
2-120		371,83	335	220 (dec.)	A
2-121		389,34	389	144-145	B
2-122		373,80	338	285(dec.)	A

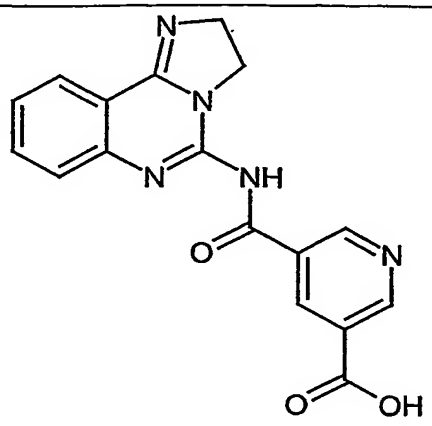
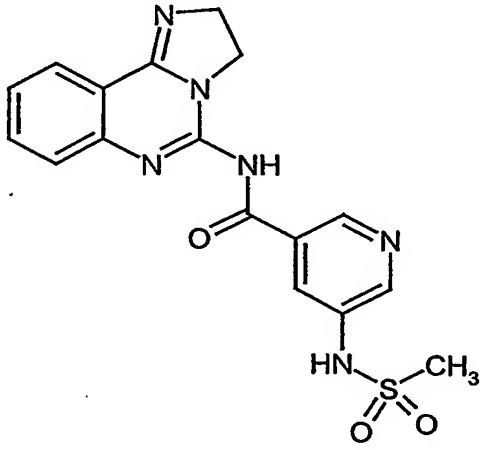
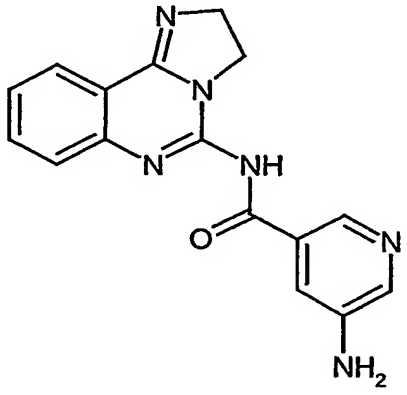
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-123		372,82	337	296	A
2-124		360,38	361	287	A
2-125		396,84	361	238	A
2-126		386,42	386	183-184	A

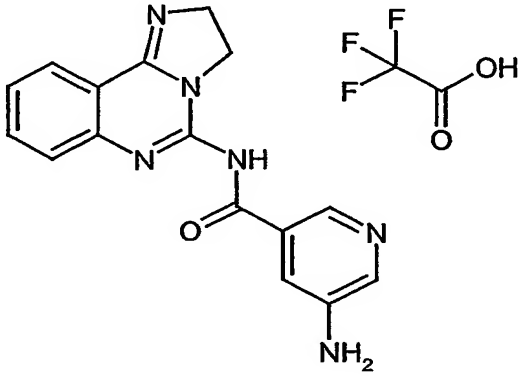
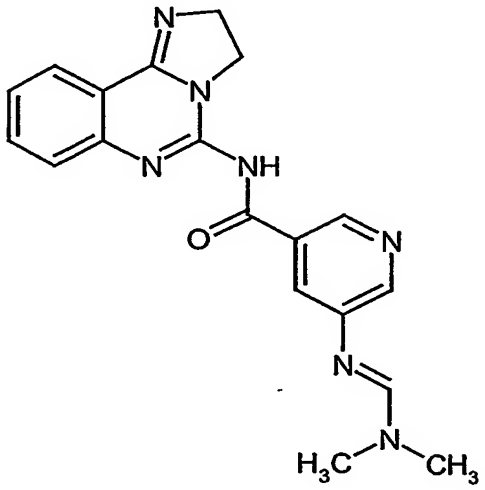
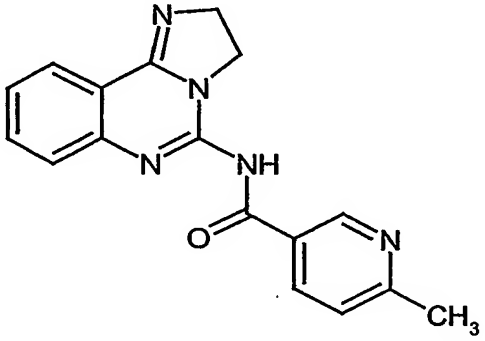
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-127		422,88	386	225 (dec.)	A
2-128		440,39	440	214 (dec.)	A
2-129		476,85	440	226 (dec.)	A
2-130		405,34	292	237-239	A

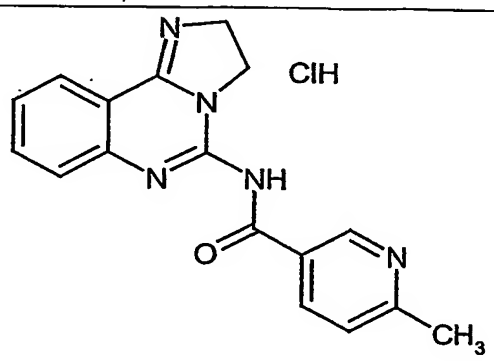
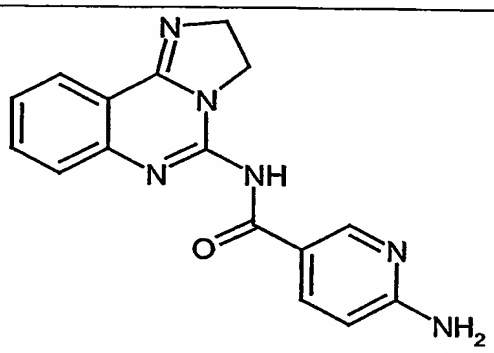
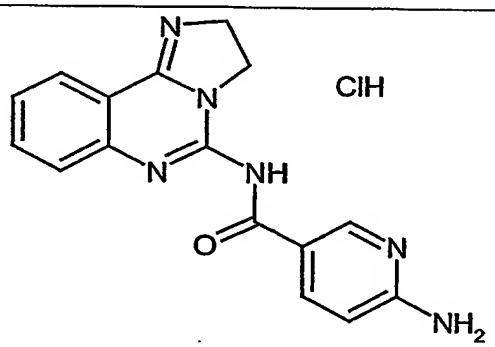
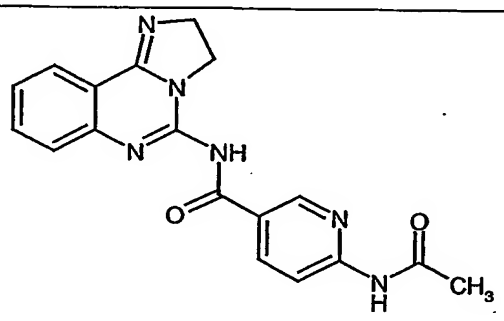
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-131		305,34	306	193 - 194	B
2-132		341,80	306	277 (dec.)	B
2-133		306,33	306	215(dec.)	B
2-134		325,76	326	198 - 199	A

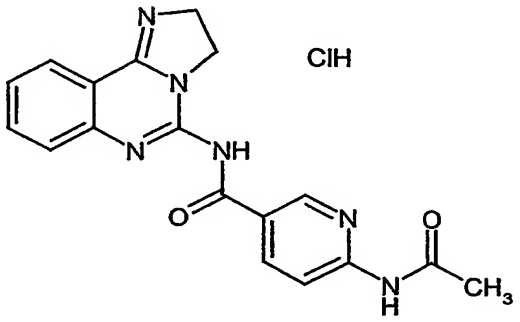
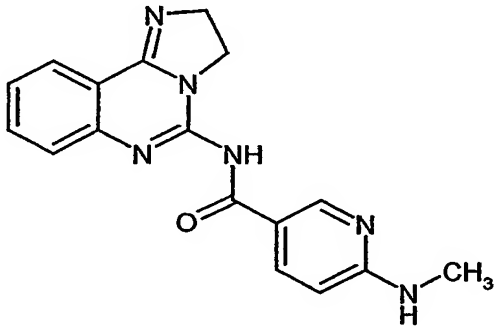
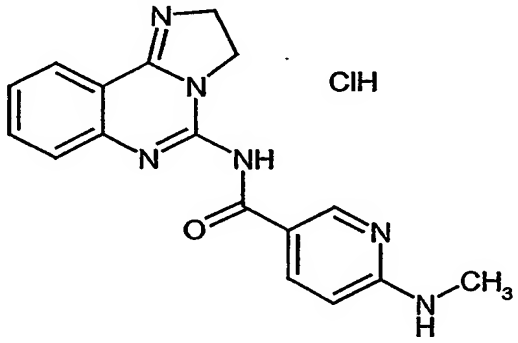
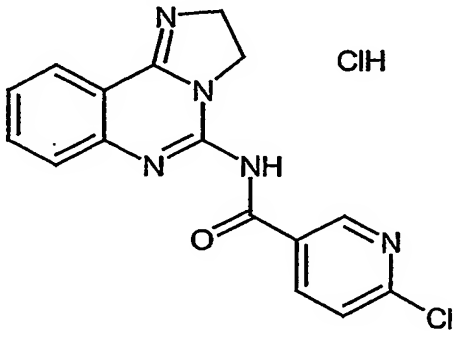
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-135		362,22	326	340 (dec.)	B
2-136		305,34	305	194-195	B
2-137		341,80	305	291 (dec.)	B
2-138		307,31	307	273(dec.)	A

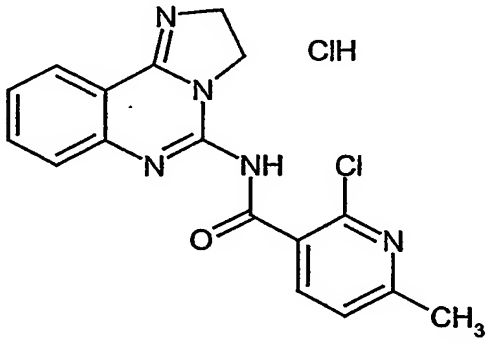
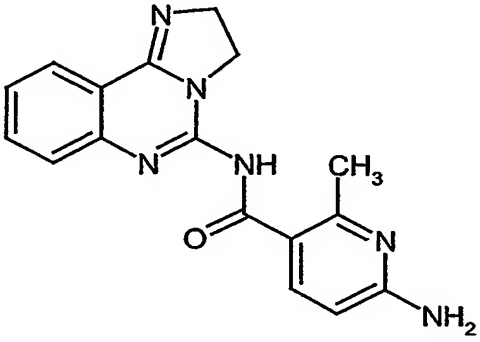
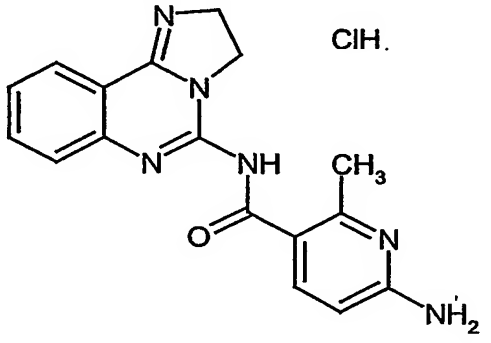
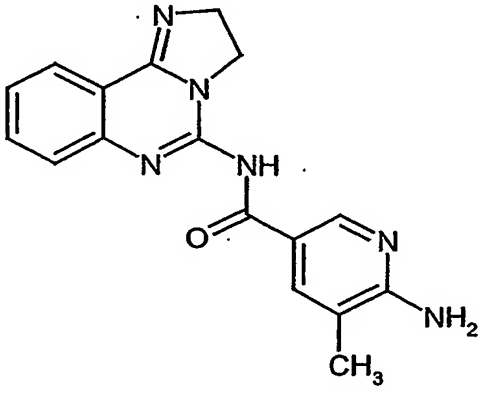
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-139		343,78	307	296-297	A
2-140		321,34	321	219 (dec.)	B
2-141		357,80	321	272(dec.)	B

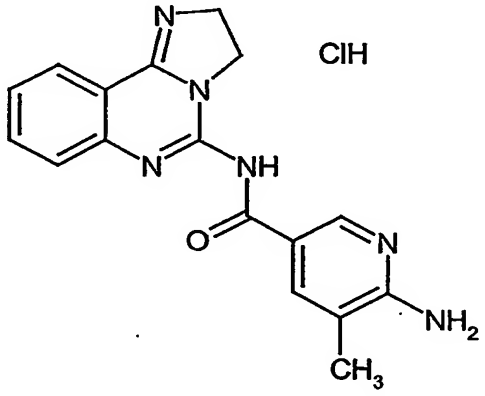
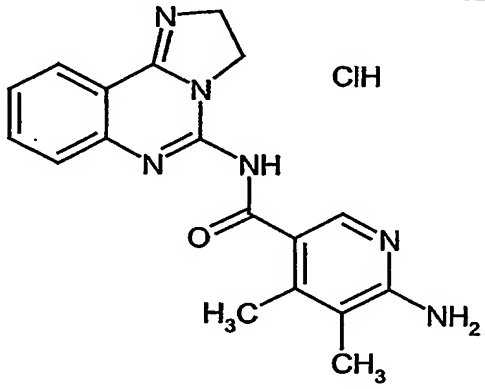
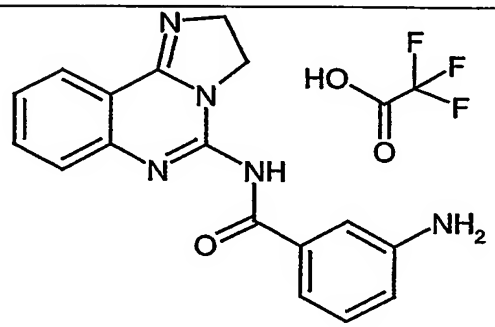
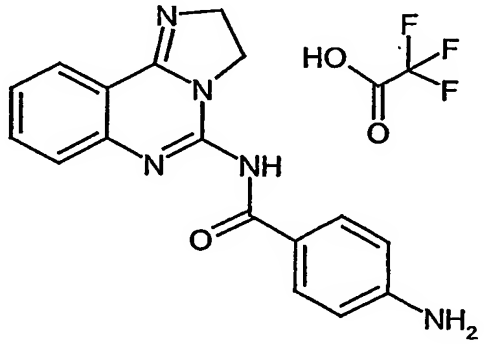
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-142		335,32	336	358-359	B
2-143		384,42	385	265-269	A
2-144		306,33	307	263-266	A

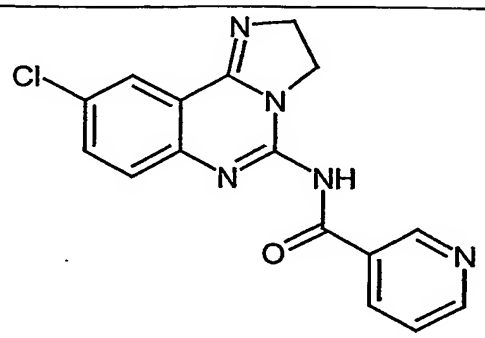
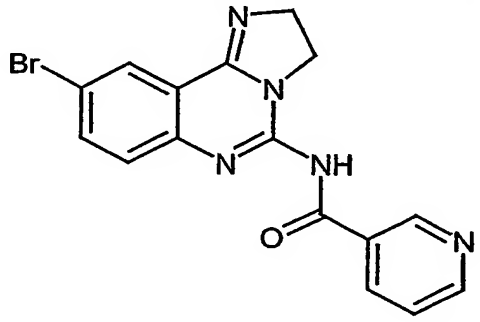
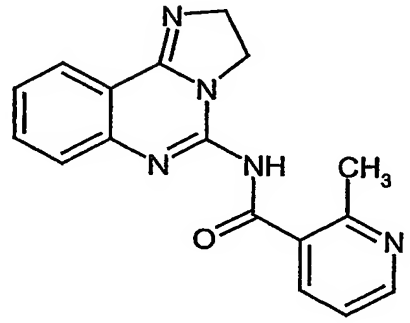
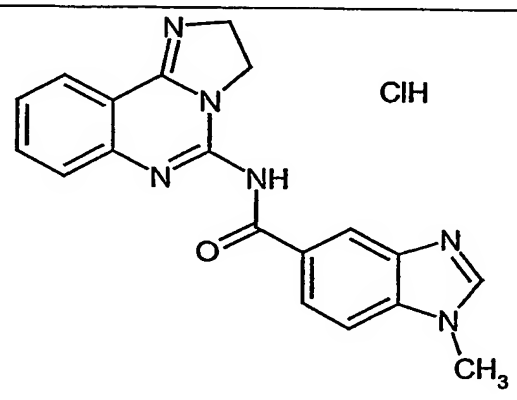
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-145		420,35	307	229(dec.)	B
2-146		361,41	362	219(dec.)	B
2-147		305,34	306	195 - 196	A

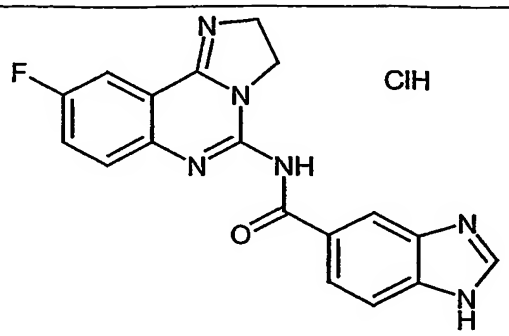
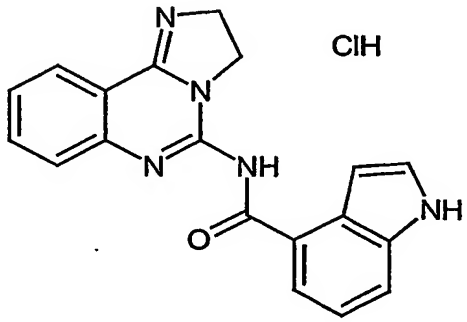
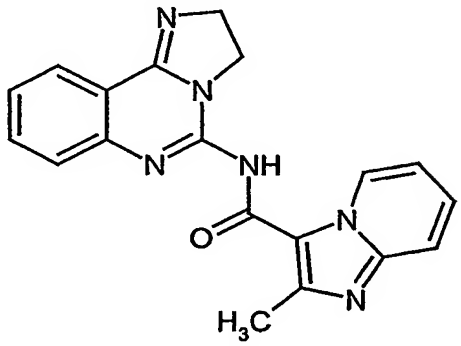
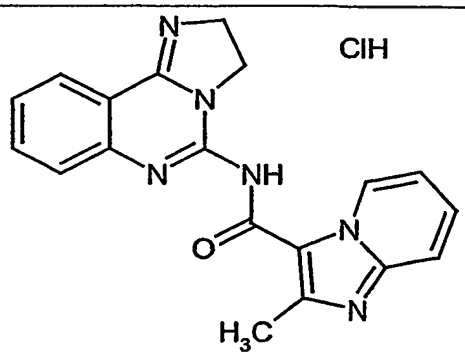
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-148		341,80	306	310 (dec.)	A
2-149		306,33	307	> 300	A
2-150		342,79	307	290 (dec.)	A
2-151		348,37	349	320 (dec.)	A

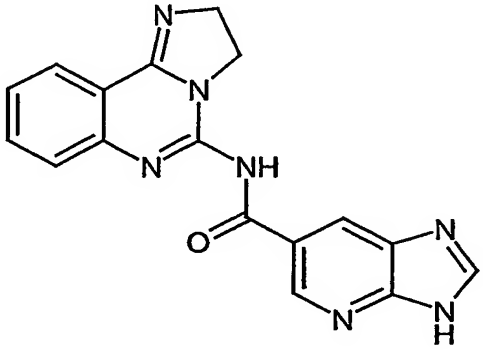
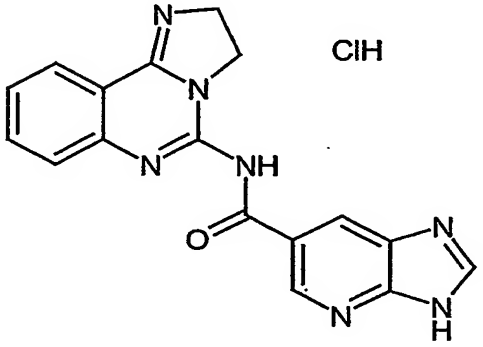
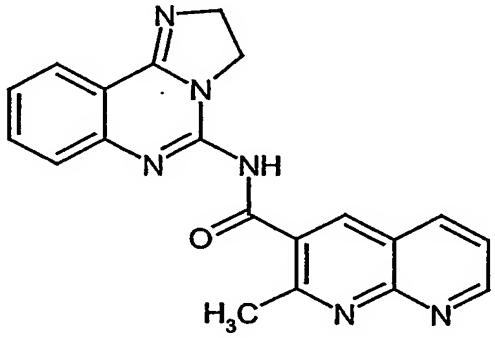
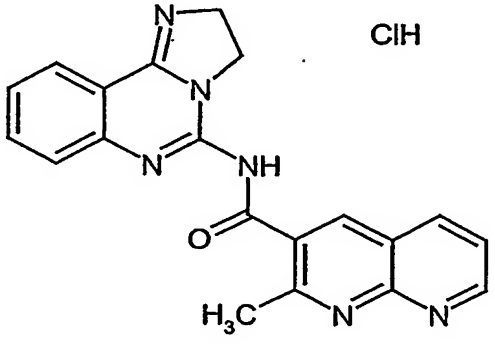
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-152		384,83	349	312 (dec.)	A
2-153		320,36	320	196-197	B
2-154		356,82	320	300(dec.)	B
2-155		362,22	326	324 (dec.)	B

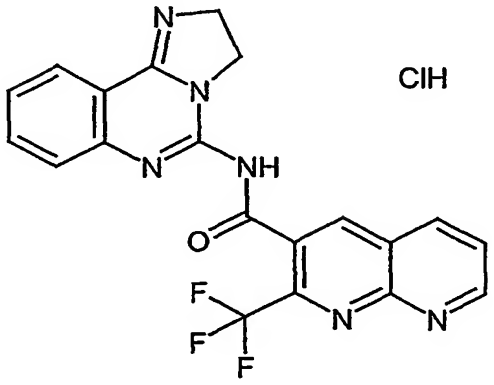
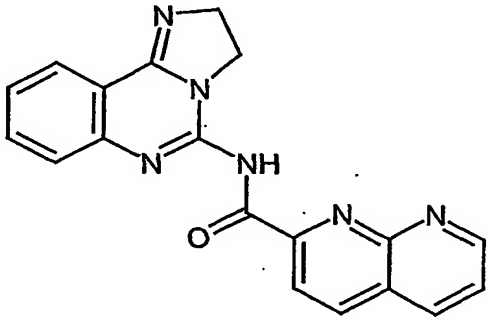
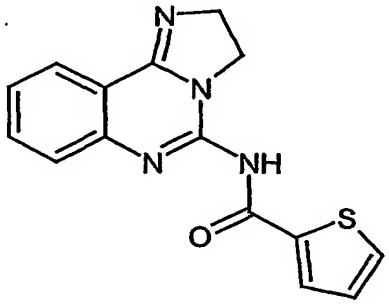
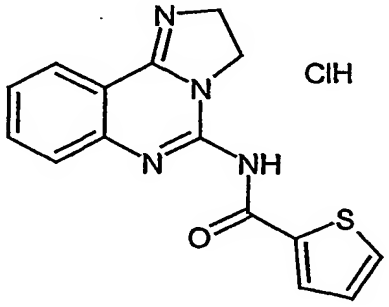
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-156		376,25	340	287 (dec.)	B
2-157		320,36	321	146-148	B
2-158		356,82	321	289(dec.)	B
2-159		320,36	320	246-247	B

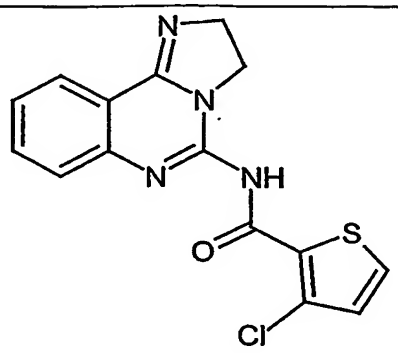
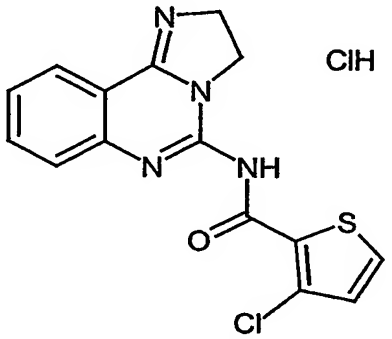
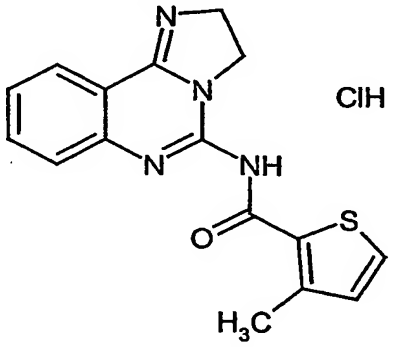
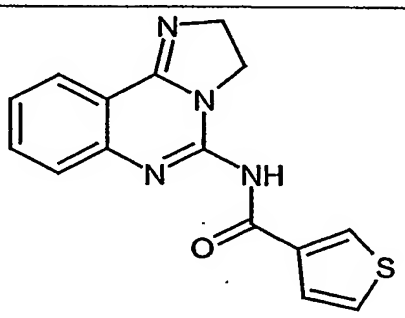
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-160		356,82	320	311(dec.)	B
2-161		370,84	334	298(dec.)	B
2-162		419,37	306	191(dec.)	B
2-163		419,37	306	232(dec.)	B

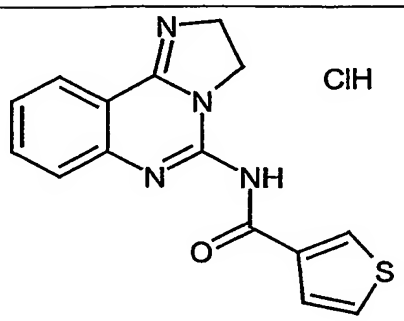
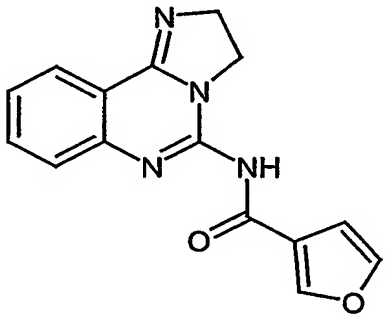
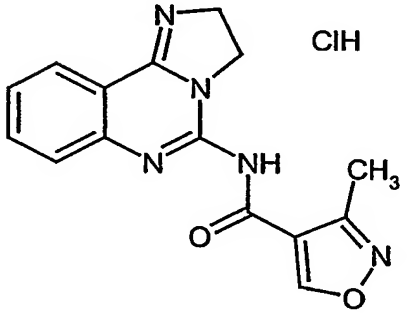
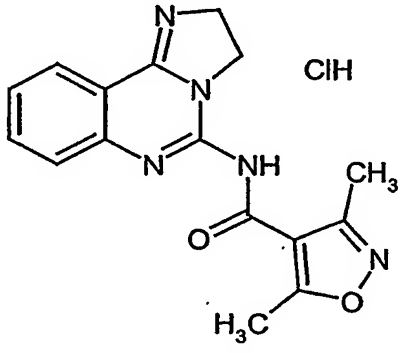
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-164		461,40	348	247(dec.)	A
2-165		328,76	292	291(dec.)	B
2-166		444,38	331	221(dec.)	A
2-167		380,84	345	333(dec.)	B

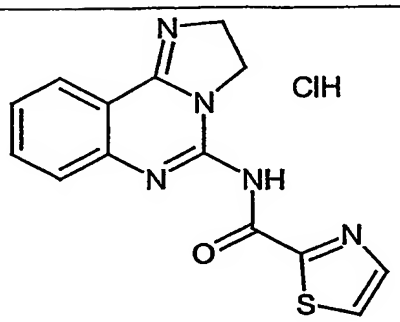
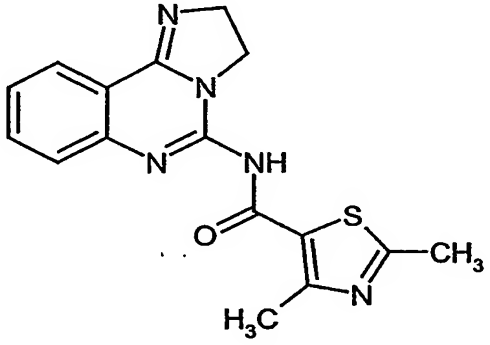
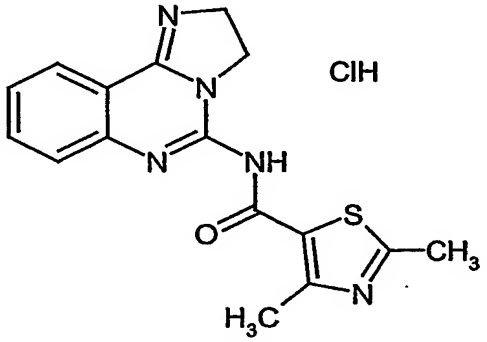
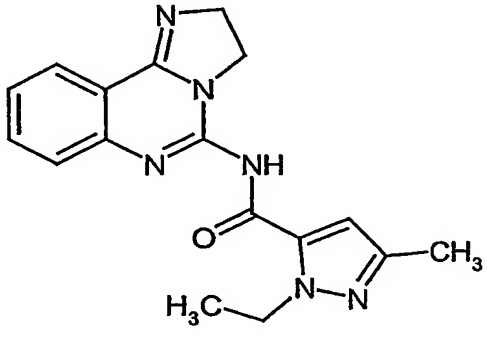
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-168		329,36	330	160(dec.)	B
2-169		365,83	330	295(dec.)	B
2-170		344,38	345	277-279	B
2-171		380,84	345	328(dec.)	B

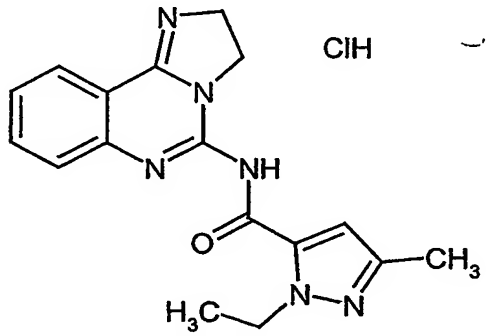
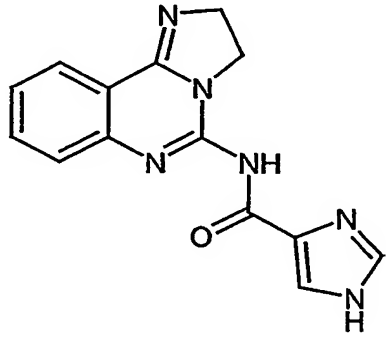
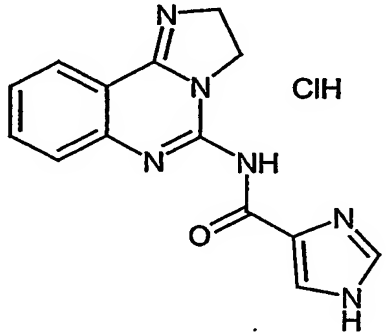
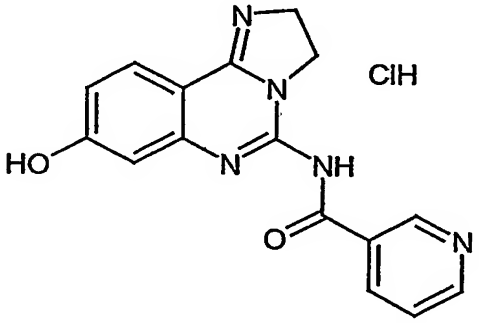
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-172		331,34	332	>300	A
2-173		367,80	332	287(dec.)	A
2-174		356,39	356	296(dec.)	B
2-175		392,85	356	270(dec.)	B

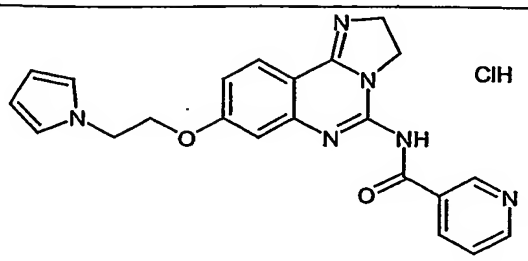
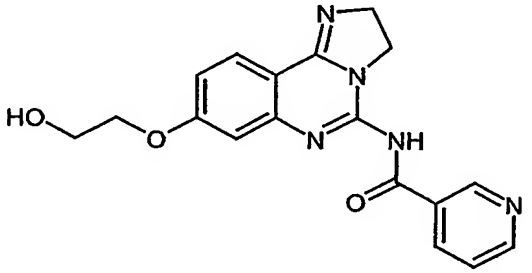
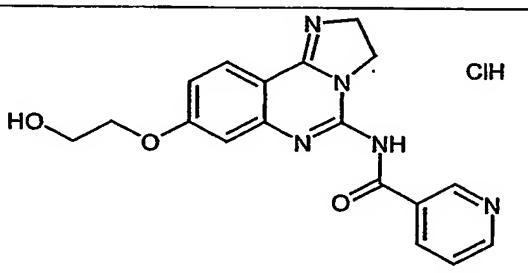
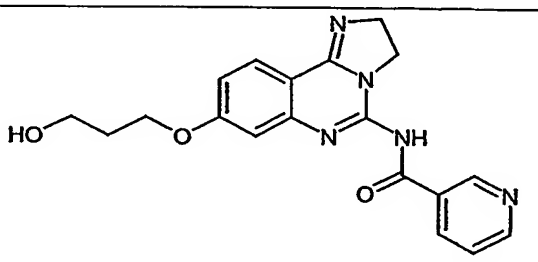
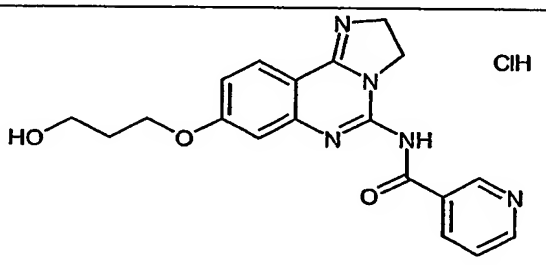
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-176		446,82	410	248-249	B
2-177		342,36	342	275(dec.)	B
2-178		296,35	297	187 - 188	B
2-179		332,81	297	310 (dec.)	A

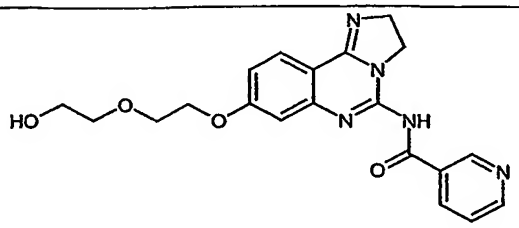
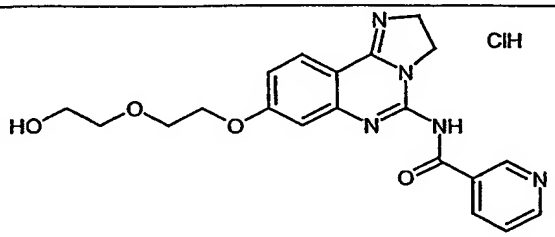
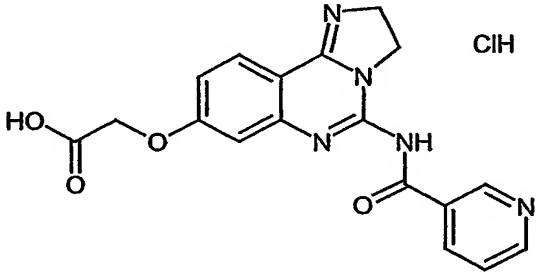
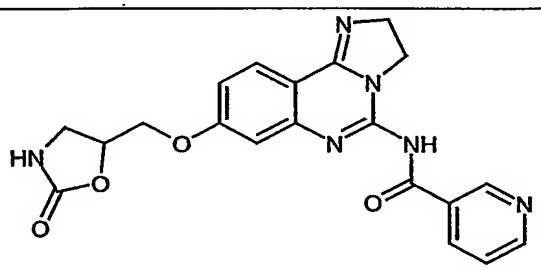
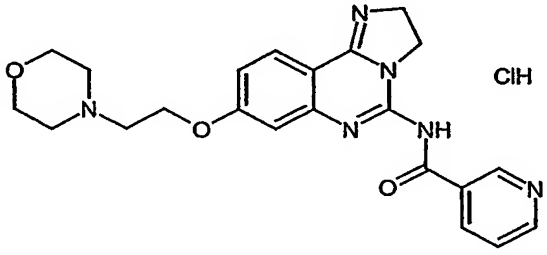
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-180		330,80	330	198-199	B
2-181		367,26	330	298(dec.)	B
2-182		346,84	310	>250	B
2-183		296,35	297	167 (dec.)	B

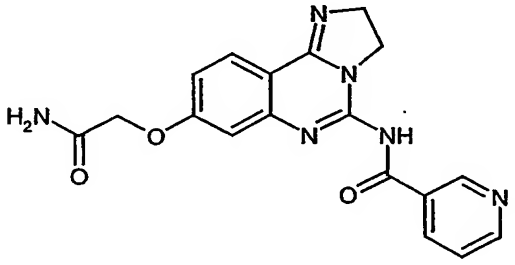
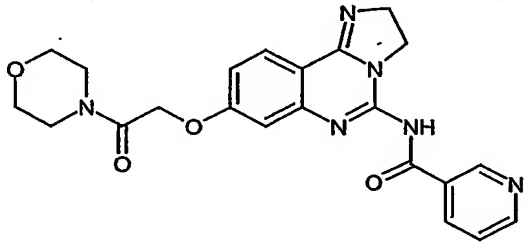
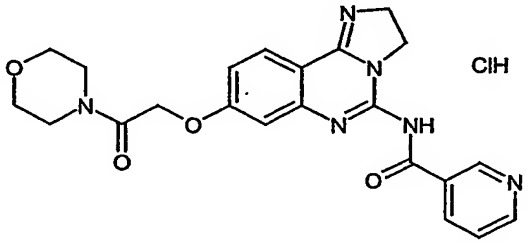
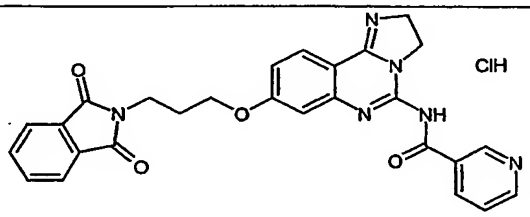
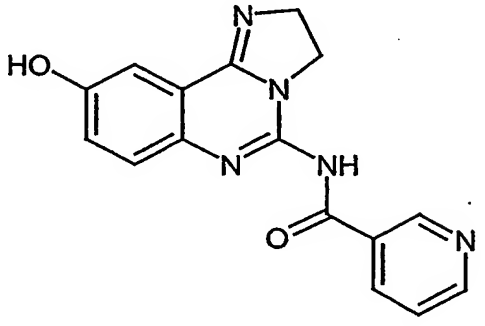
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-184		332,81	297	297 (dec.)	B
2-185		280,29	280	217-218	B
2-186		331,76	295	285(dec.)	B
2-187		345,79	309	280-281	B

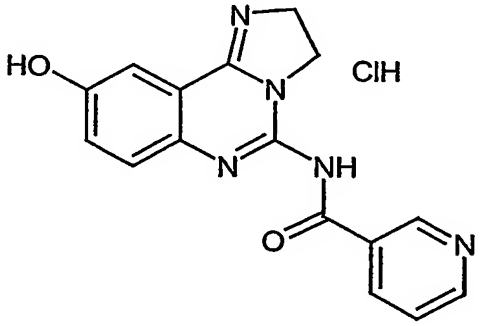
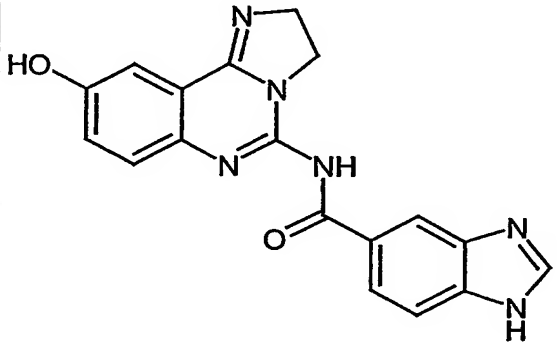
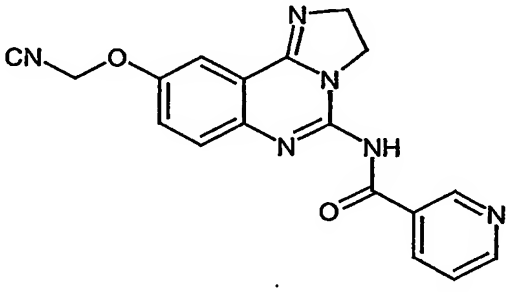
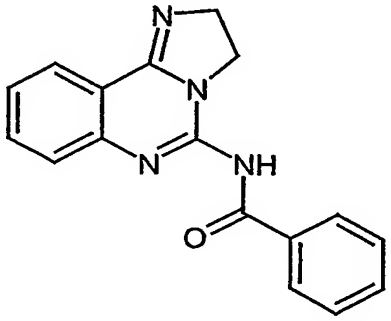
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-188		333,80	298	306(dec.)	B
2-189		325,39	326	243 (dec.)	B
2-190		361,86	326	289 - 290	A
2-191		322,37	322	207-208	B

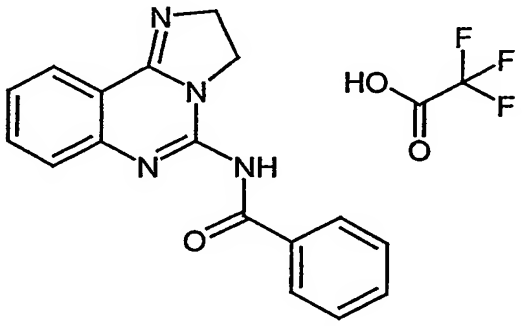
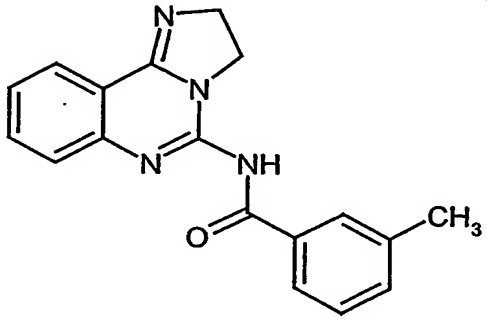
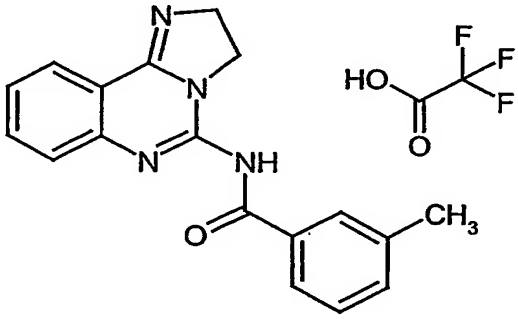
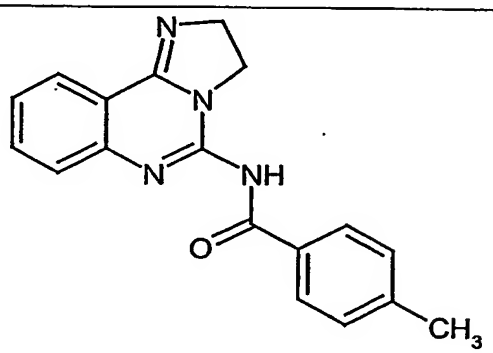
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-192		358,83	322	271-272	B
2-193		280,29	281	265 (dec.)	B
2-194		316,75	281	309 - 310	B
2-195		343,78	308	270-274(dec.)	B

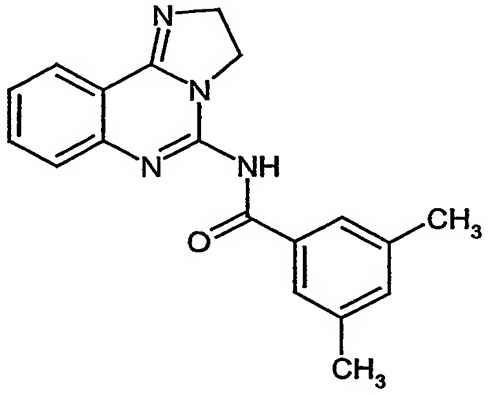
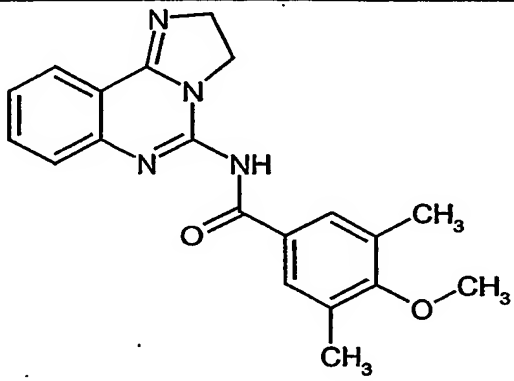
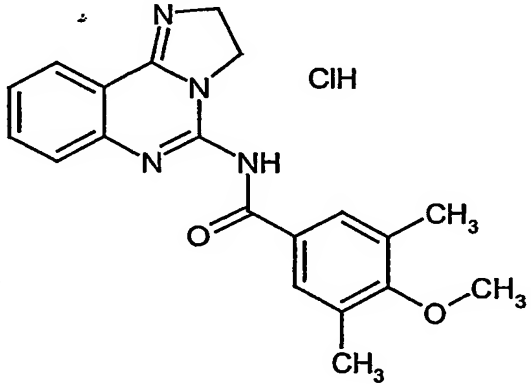
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-196		436,90	401	239	B
2-197		351,37	352	210-215(dec.)	B
2-198		387,83	352	249(dec.)	B
2-199		365,39	366	127	A
2-200		401,86	366	243(dec.)	B

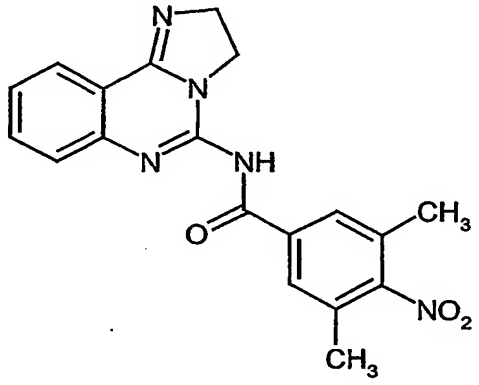
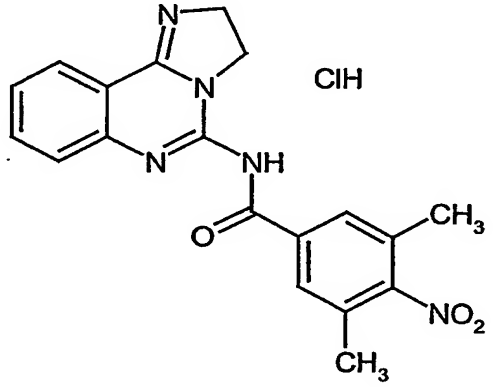
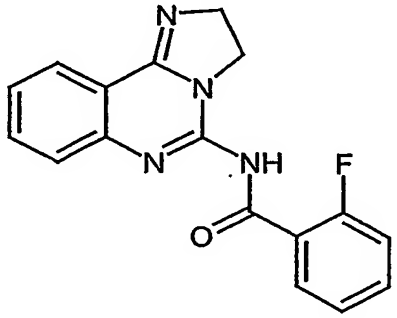
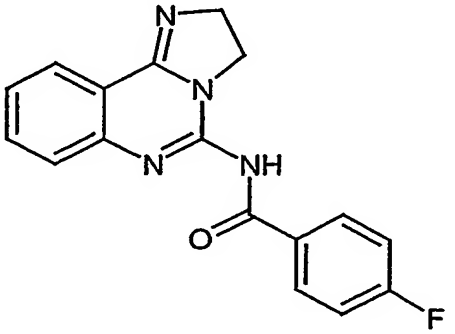
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-201		395,42	396	181	B
2-202		431,88	396	229(dec.)	B
2-203		401,81	366	231(dec.)	B
2-204		406,40	407	265-269(dec.)	B
2-205		456,94	421	243-247(dec.)	B

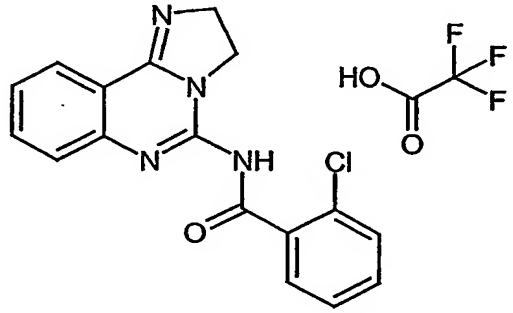
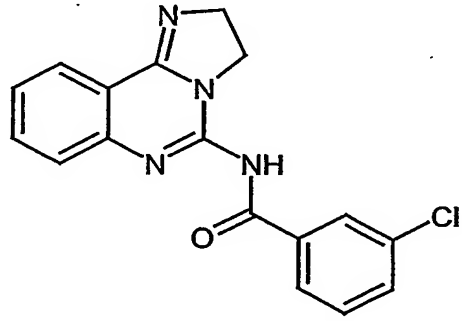
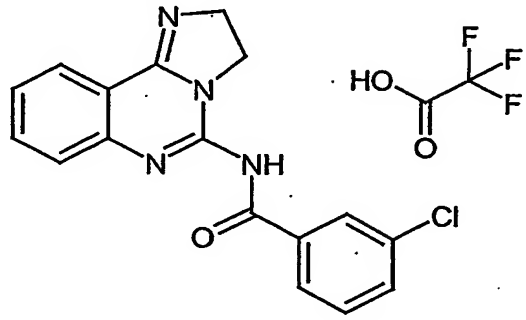
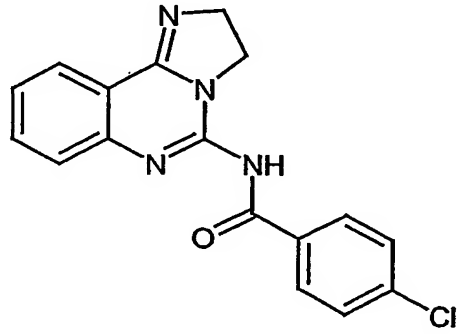
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-206		364,37	365	296	B
2-207		434,46	435	232-236(dec.)	B
2-208		470,92	435	227	B
2-209		530,98	495	247	A
2-210		307,31	308	>300	B

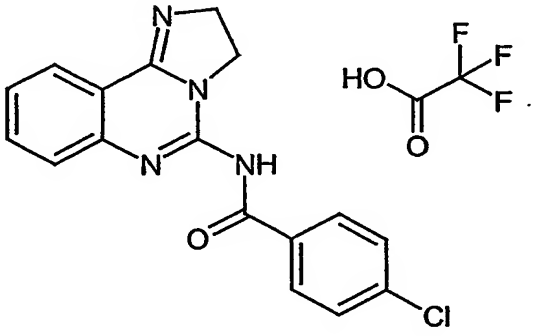
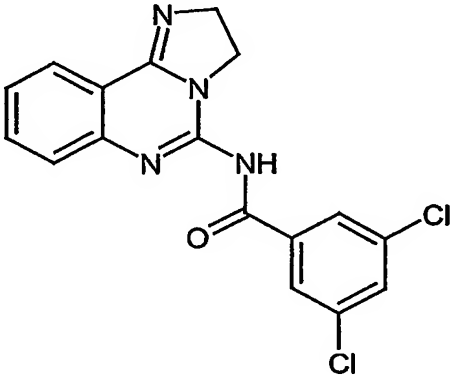
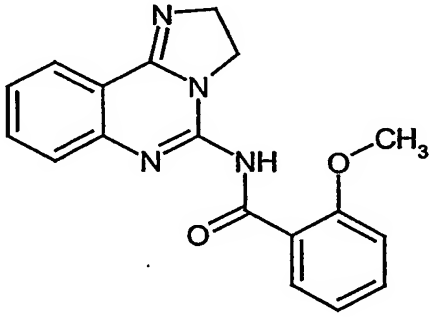
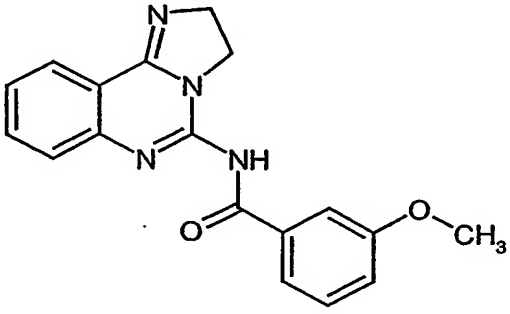
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-211		343,78	308	>300	A
2-212		346,35	347	296(dec.)	B
2-213		346,35	347	209	B
2-214		290,33	291	201-203(dec.)	C

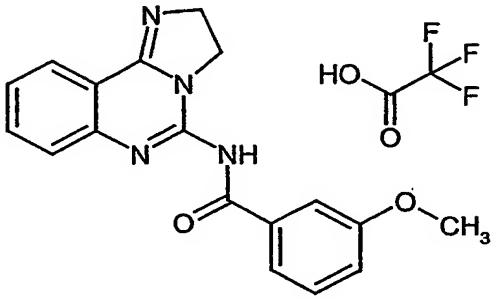
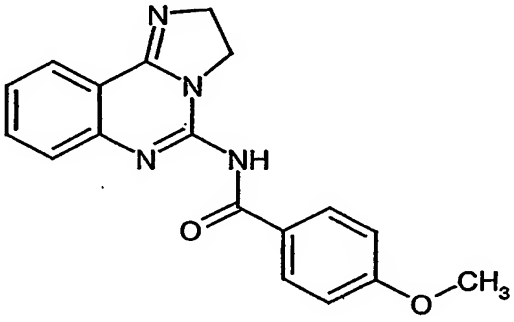
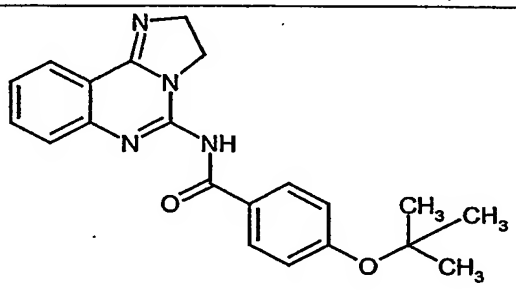
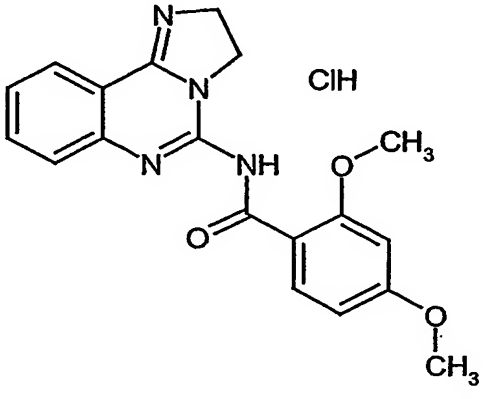
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-215		404,35	291	238-242	B
2-216		304,35	305	201-203	D
2-217		418,38	305	239-241	B
2-218		304,35	305	185-186	D

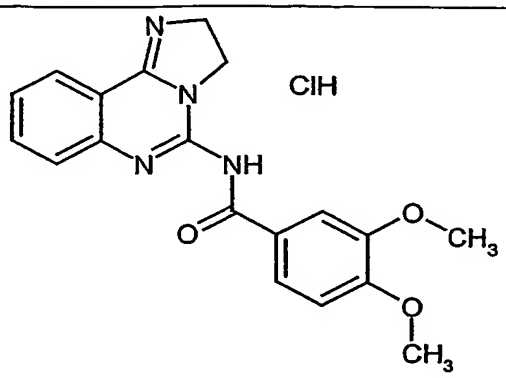
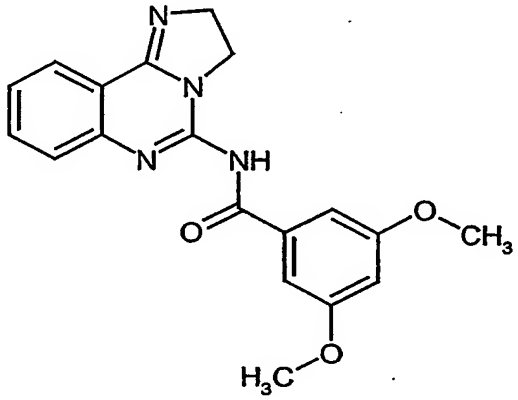
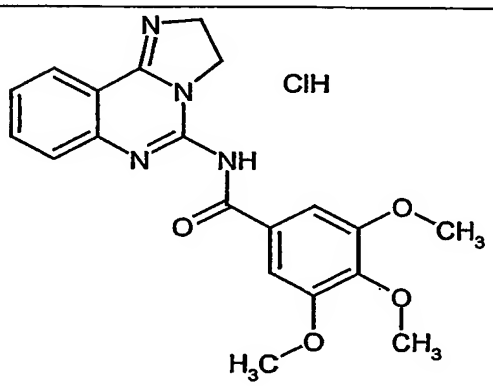
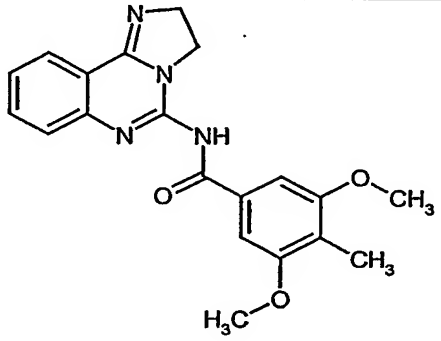
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-219		318,38	319	246-248	D
2-220		348,41	349	216-218	D
2-221		384,87	349	288 (dec.)	D

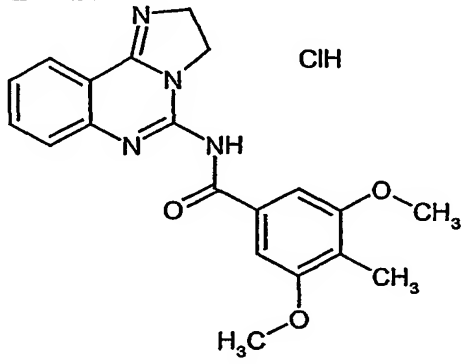
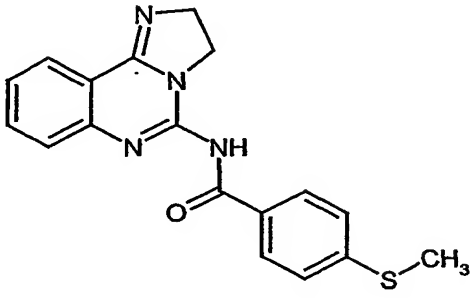
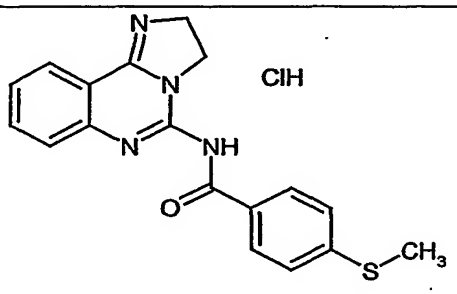
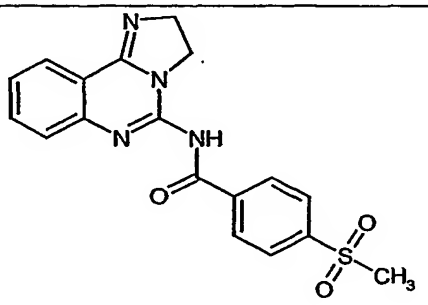
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-222		363,38	364	277 (dec.)	D
2-223		399,84	364	313 (dec.)	D
2-224		308,32	309	202-204	C
2-225		308,32	309	210-212	D

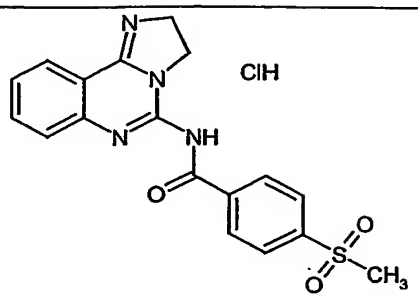
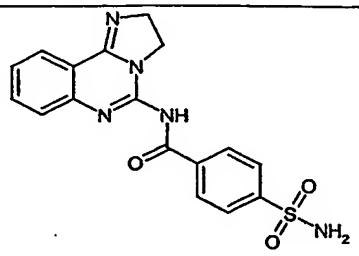
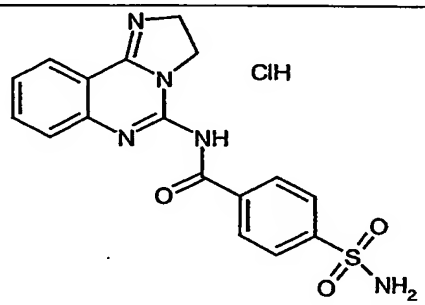
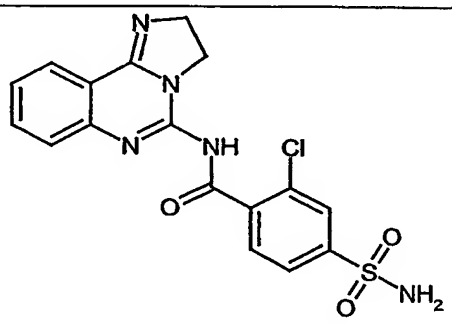
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-226		438,80	325	221-224	D
2-227		324,77	325	196-197	D
2-228		438,80	325	233-235	C
2-229		324,77	325	226-228	D

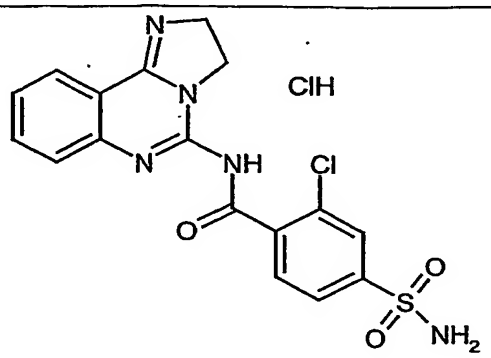
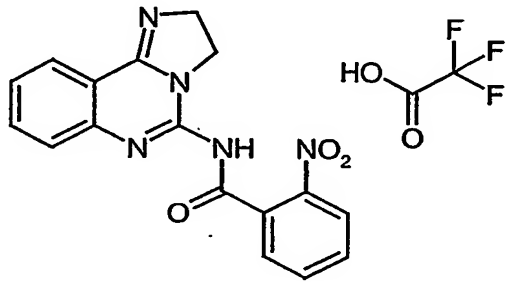
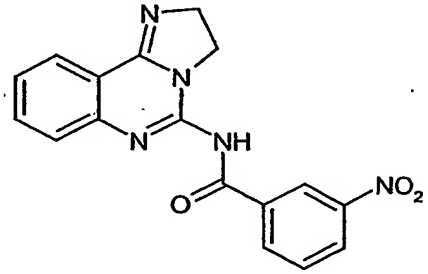
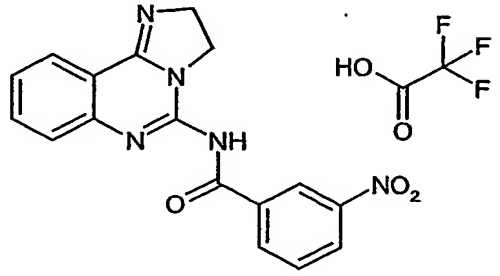
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-230		438,80	325	243-245	D
2-231		359,22	358	268-269	D
2-232		320,35	321	185-187	D
2-233		320,35	321	202-204	D

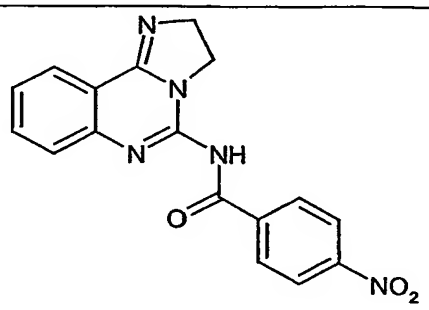
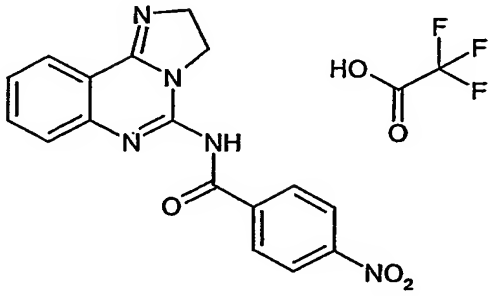
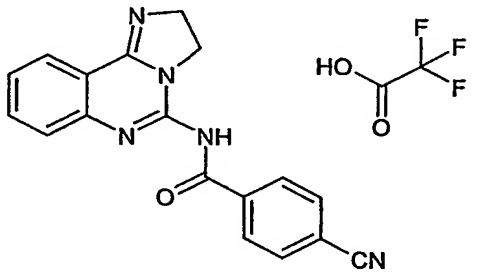
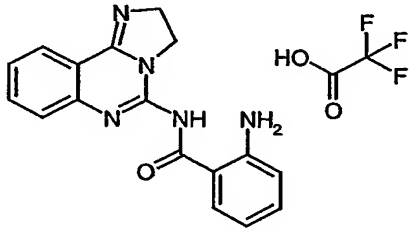
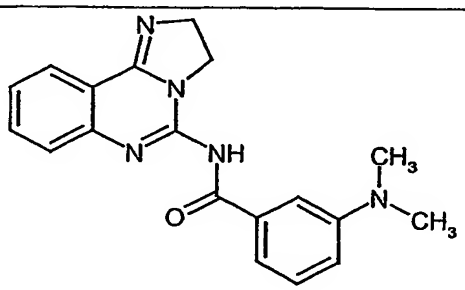
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-234		434,38	321	209-211	C
2-235		320,35	321	300 (dec.)	D
2-236		362,44	363	>410	D
2-237		386,84	351	259 (dec.)	D

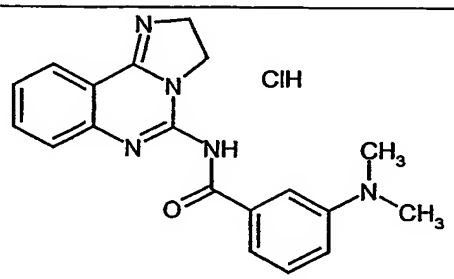
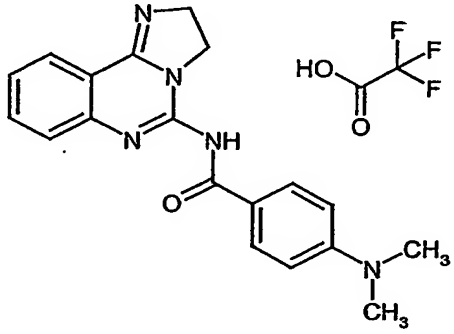
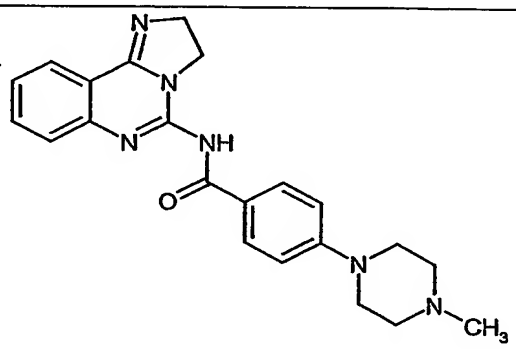
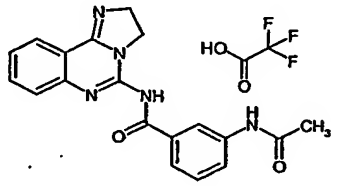
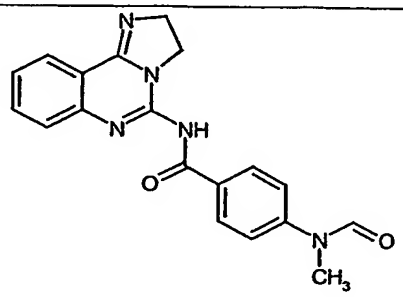
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-238		386,84	351	274 (dec.)	B
2-239		350,38	351	330 (dec.)	D
2-240		416,87	381	291 (dec.)	D
2-241		364,41	365	248 (dec.)	D

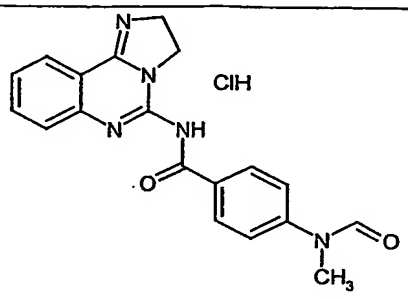
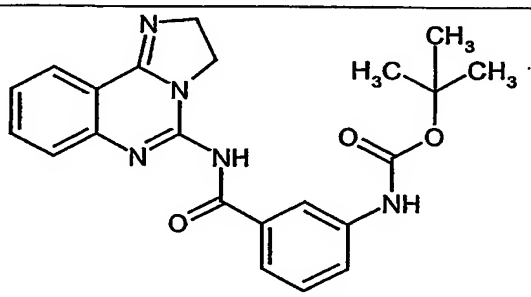
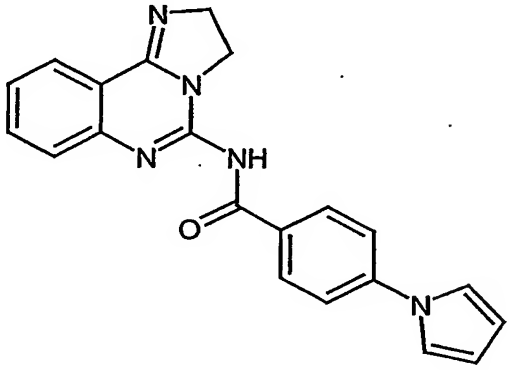
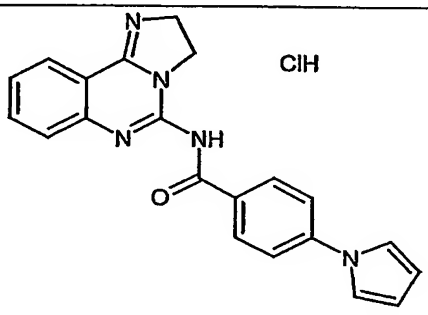
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-242		400,87	365	321 (dec.)	D
2-243		336,42	337	169-170	D
2-244		372,88	337	292 (dec.)	D
2-245		368,42	369	278 (dec.)	D

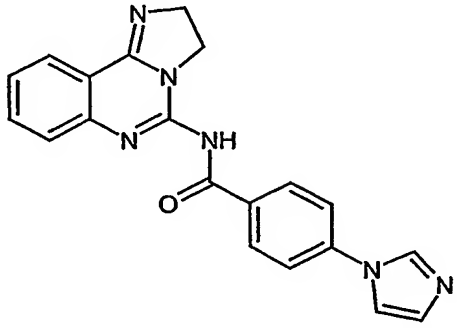
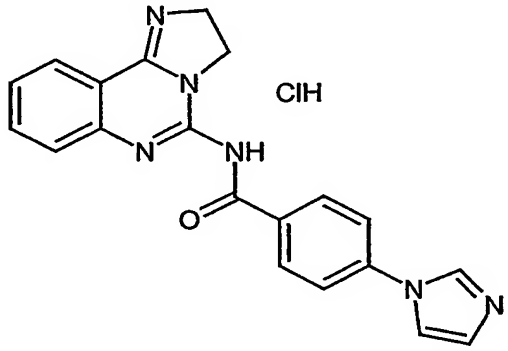
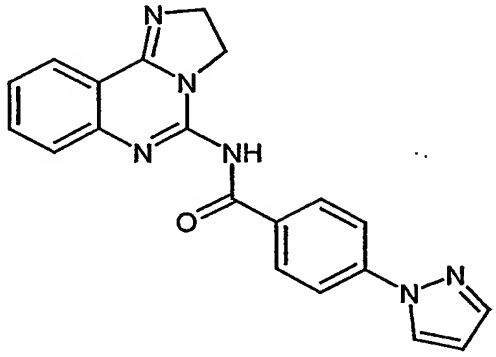
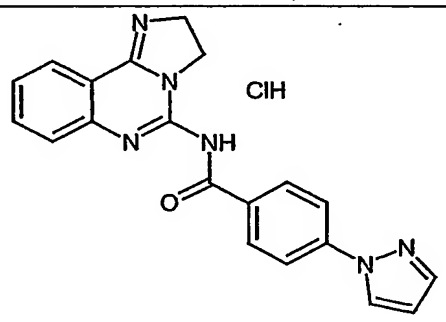
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-246		404,88	369	320 (dec.)	D
2-247		369,40	370	278 (dec.)	C
2-248		405,87	370	308 (dec.)	C
2-249		403,85	403	240 (dec.)	D

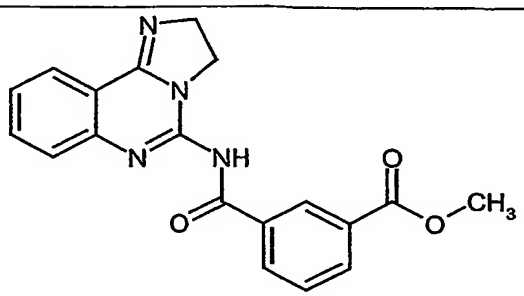
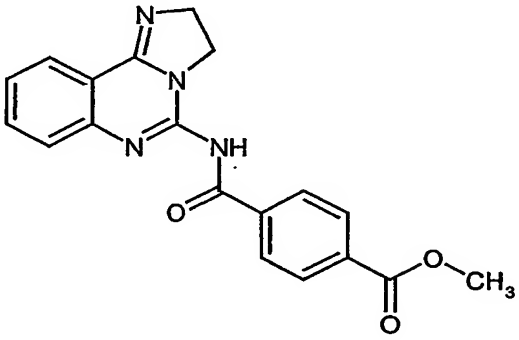
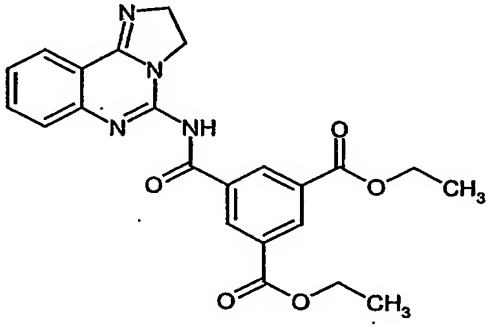
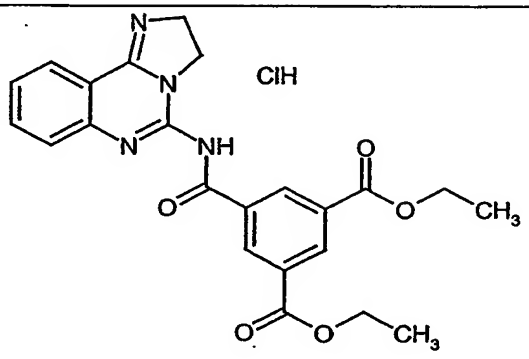
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-250		440,31	403	300 (dec.)	D
2-251		449,35	336	198-200	D
2-252		335,32	334	265-267	D
2-253		449,35	336	238-239	D

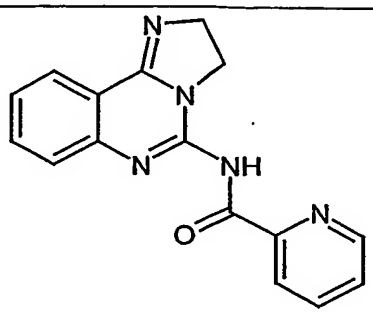
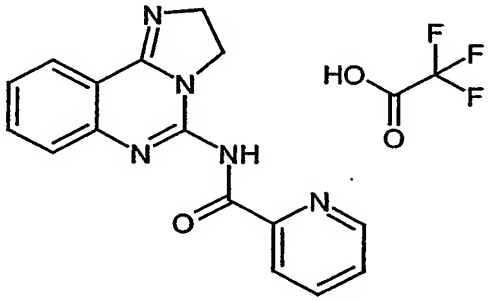
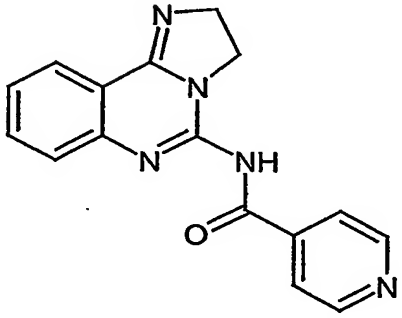
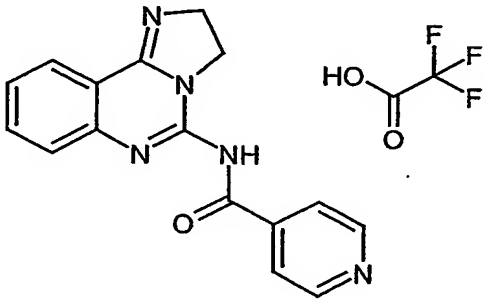
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-254		335,32	334	279-281	D
2-255		449,35	336	265 (dec.)	D
2-256		429,36	316	248-250	D
2-257		419,37	306	175 (dec.)	D
2-258		333,40	334	188-190	D

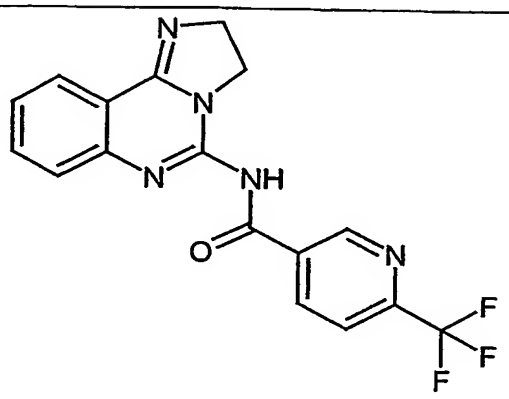
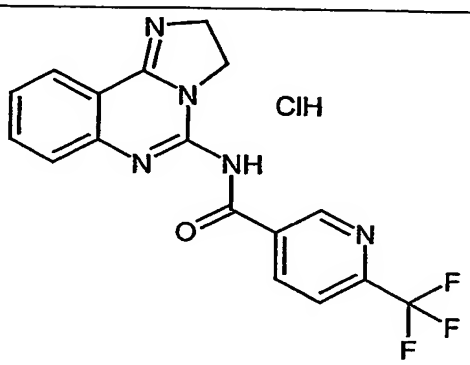
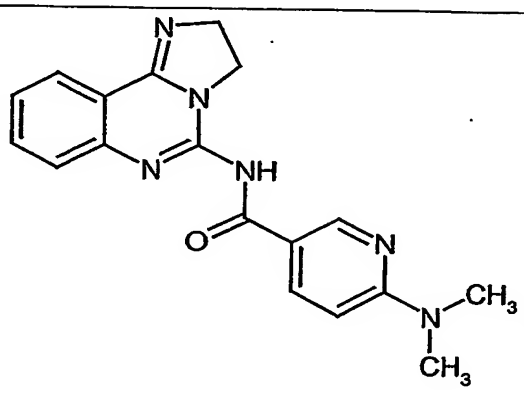
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-259		369,86	334	266 (dec.)	D
2-260		447,42	334	240 (dec.)	D
2-261		388,48	389	218-222	D
2-262		461,40	348	253(dec.)	D
2-263		347,38	348	208-210	D

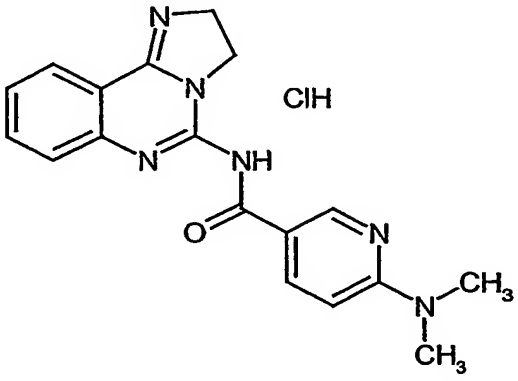
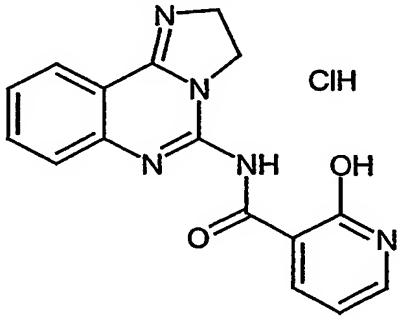
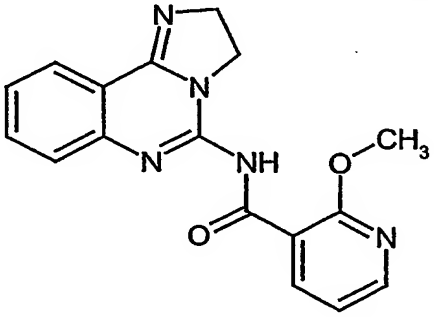
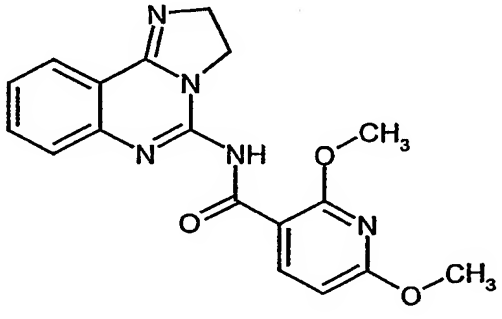
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-264		383,84	348	304 (dec.)	D
2-265		405,46	406	280 (dec.)	D
2-266		355,40	356	218-220	D
2-267		391,86	356	309 (dec.)	D

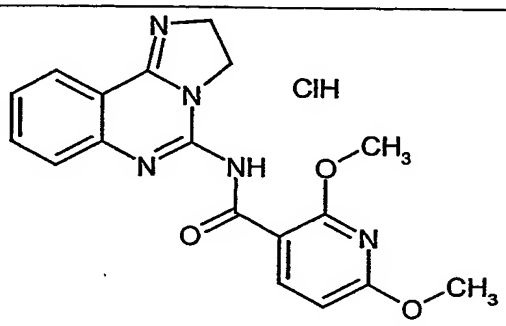
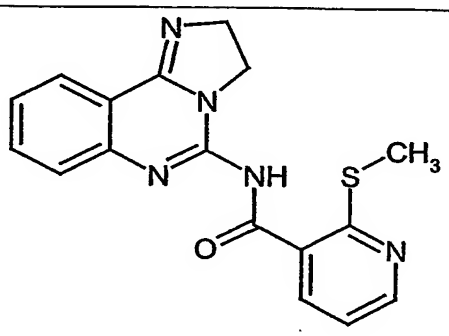
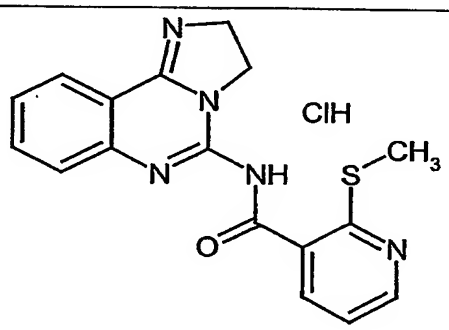
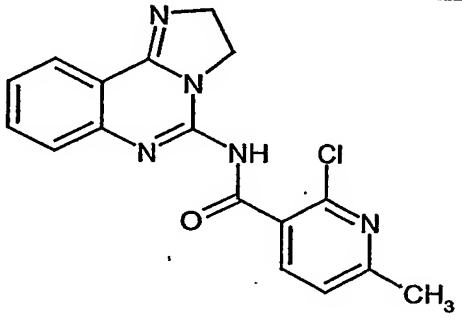
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-268		356,39	357	267 (dec.)	D
2-269		392,85	357	324(dec.)	D
2-270		356,39	357	209-211	D
2-271		392,85	357	319 (dec.)	D

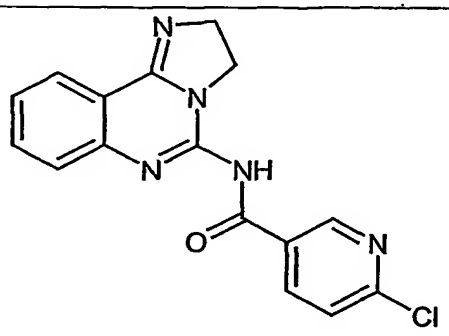
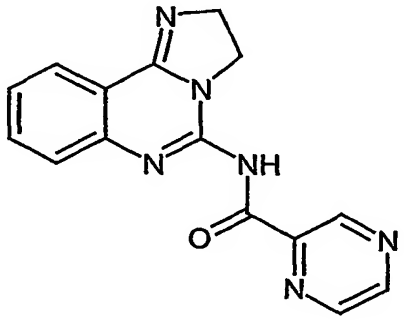
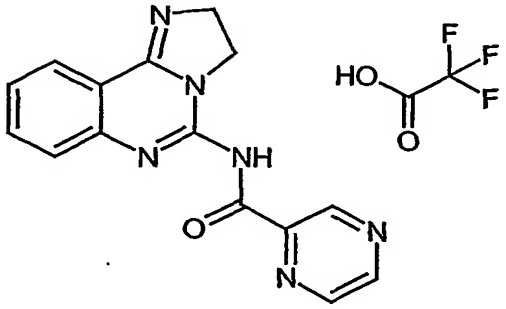
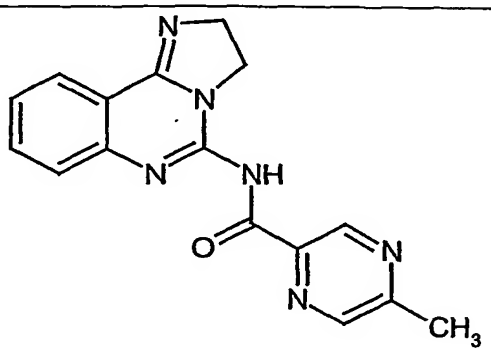
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-272		348,36	349	224-226	D
2-273		348,36	349	253-255	D
2-274		434,46	435	289 (dec.)	D
2-275		470,92	435	282	D

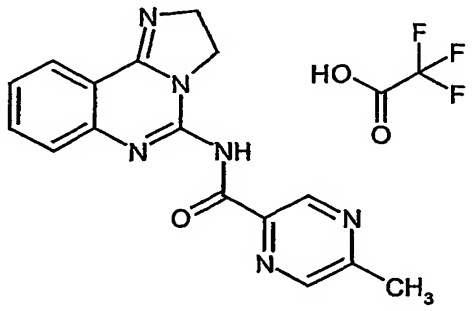
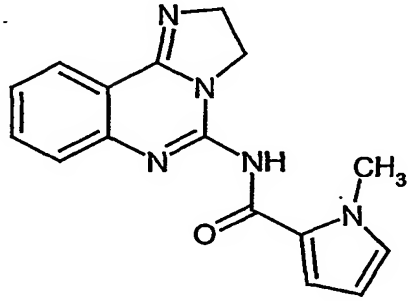
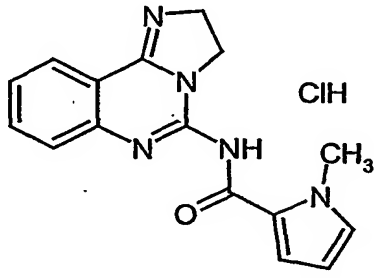
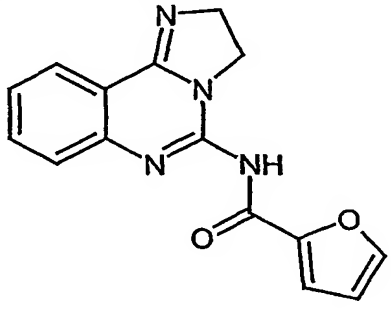
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-276		291,31	292	204 - 205	C
2-277		405,34	292	206 (dec.)	C
2-278		291,31	292	224 - 225	C
2-279		405,34	292	2310(dec.)	C

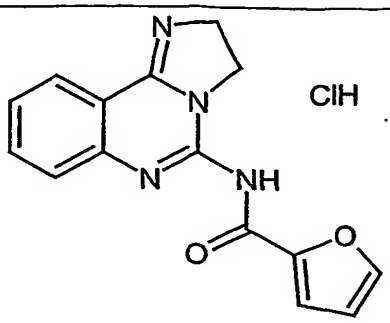
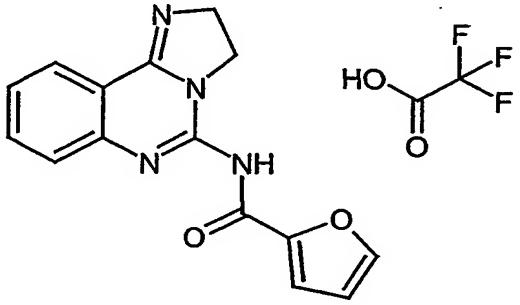
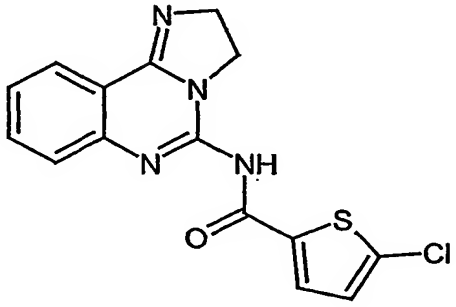
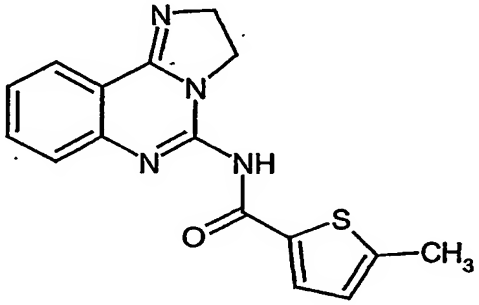
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-280		359,31	360	219 - 220	D
2-281		395,77	360	> 250	C
2-282		334,38	335	249 (dec.)	D

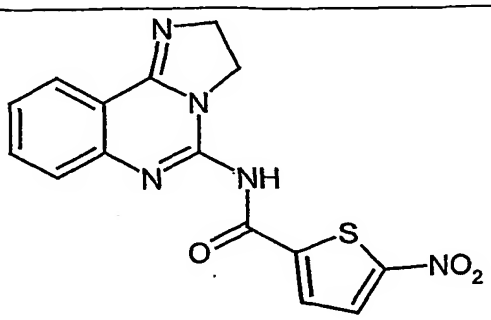
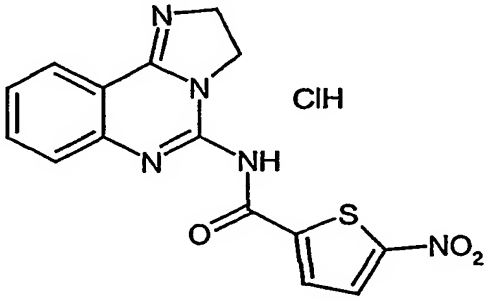
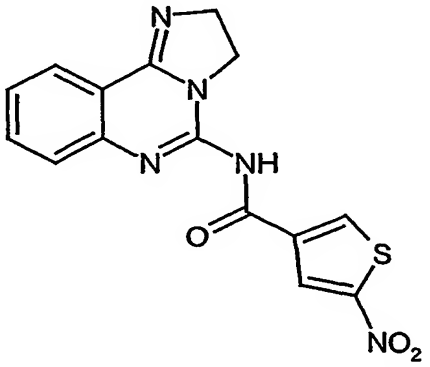
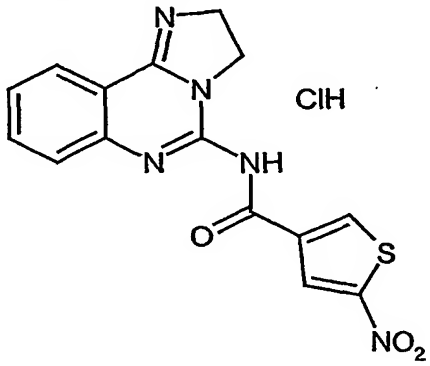
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-283		370,84	335	311 (dec.)	C
2-284		343,78	308	346 (dec.)	D
2-285		321,34	322	198 - 199	C
2-286		351,37	352	244 - 245	D

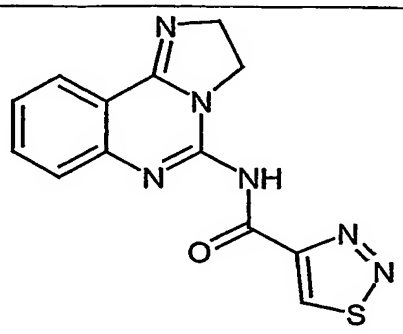
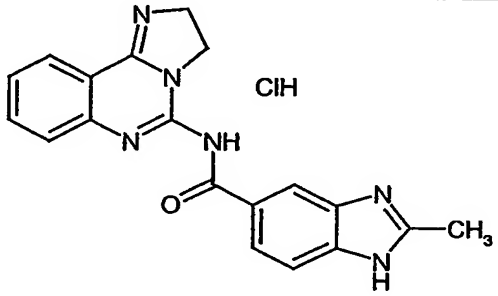
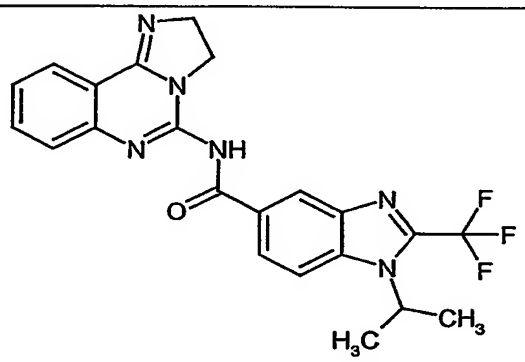
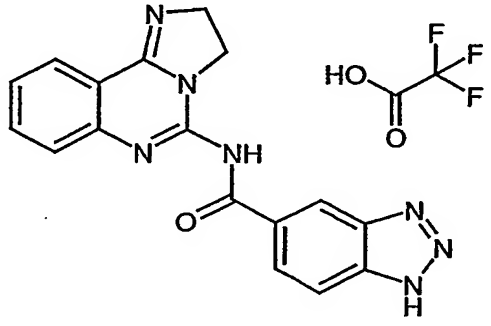
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-287		387,83	352	210 (dec.)	C
2-288		337,41	338	233 - 234	D
2-289		373,87	338	298 - 299	C
2-290		339,79	340	213 - 214	B

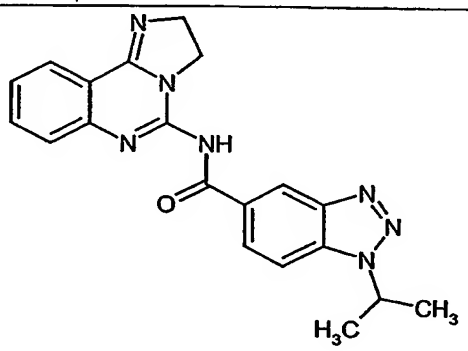
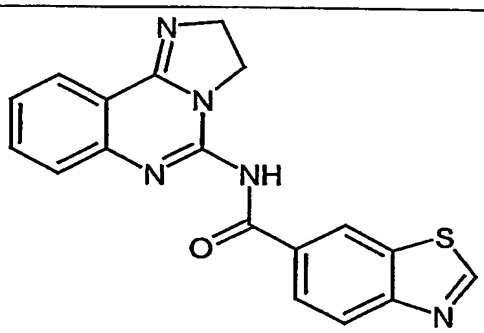
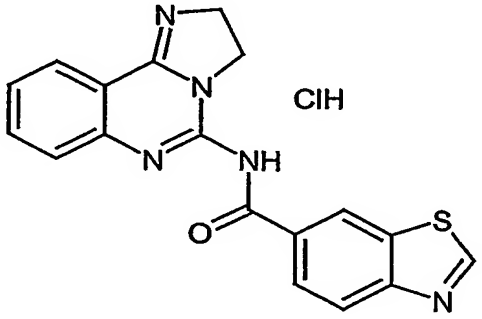
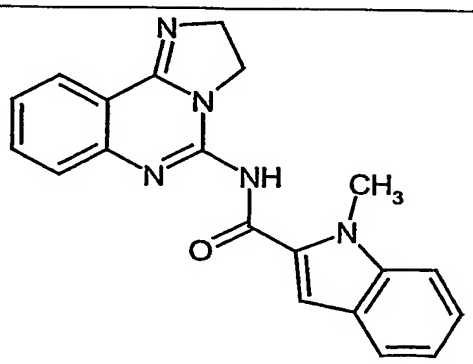
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-291		325,76	326	246 - 247	B
2-292		292,30	293	267 - 268	C
2-293		406,33	293	234 (dec.)	C
2-294		306,33	307	257 (dec.)	C

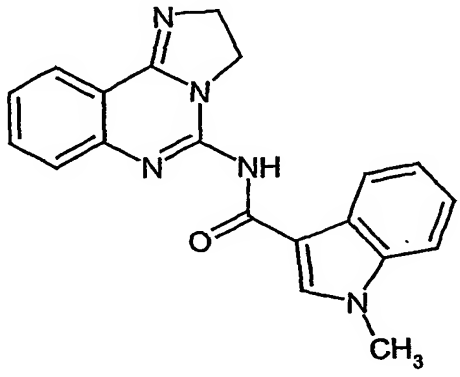
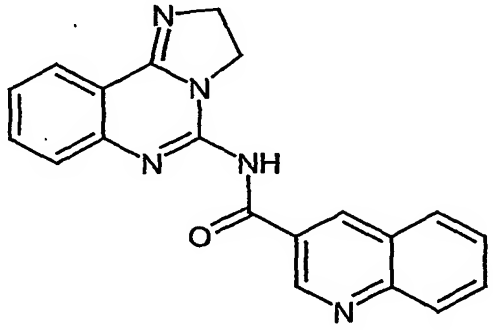
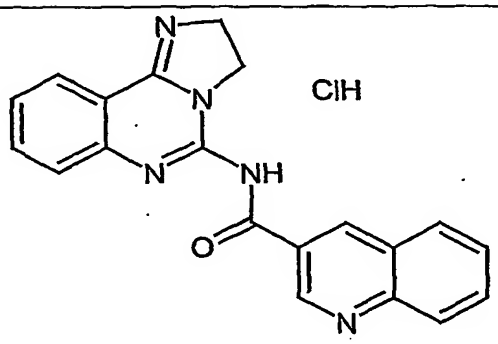
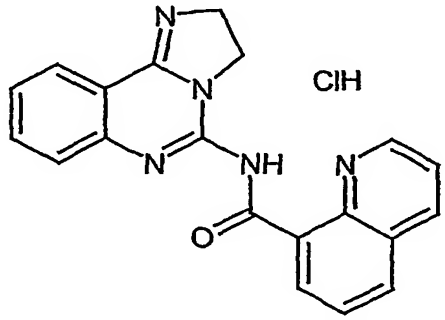
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-295		420,35	307	231 (dec.)	C
2-296		293,33	294	128 - 129	C
2-297		329,79	294	264 (dec.)	C
2-298		280,29	281	350 (dec.)	C

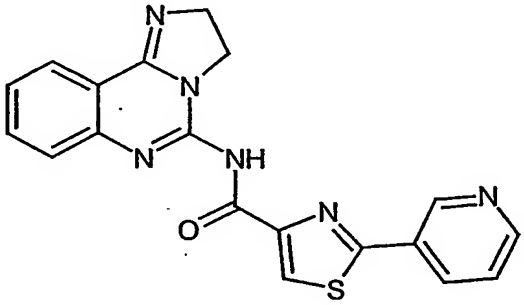
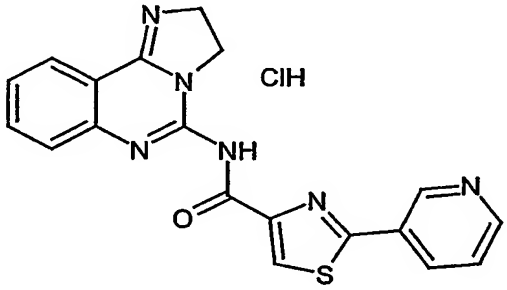
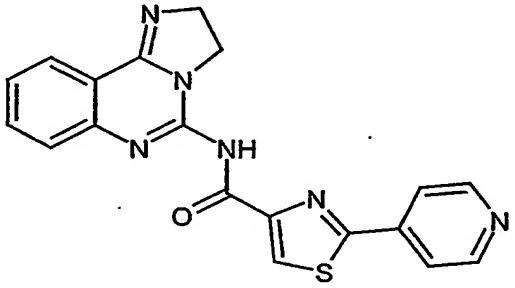
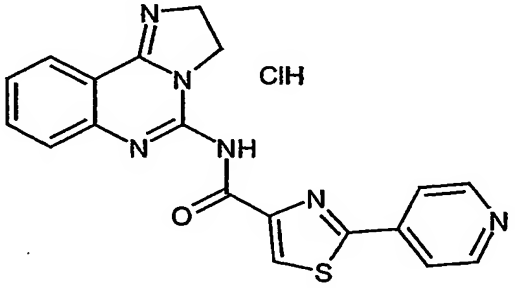
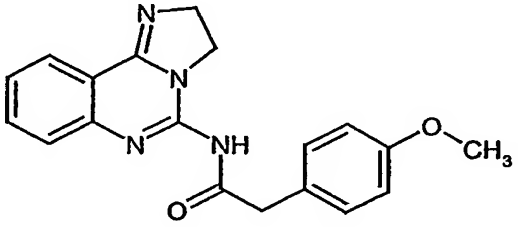
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-299		316,75	281	311 (dec.)	C
2-300		394,31	281	230-232	B
2-301		330,80	331	198 (dec.)	D
2-302		310,38	311	192 - 193	C

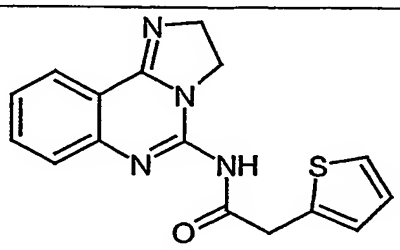
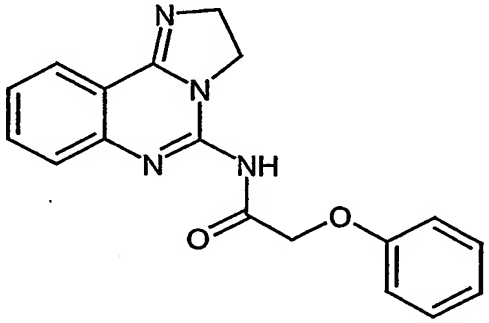
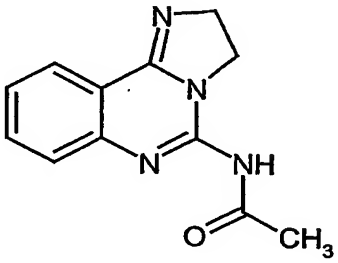
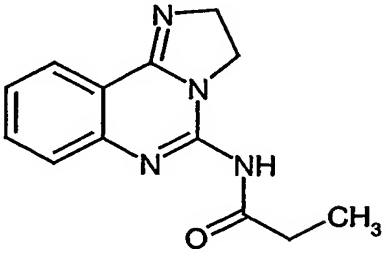
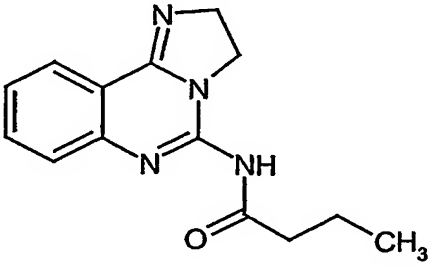
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-303		341,35	342	286 - 287	D
2-304		377,81	342	300 (dec.)	D
2-305		341,35	342	269 - 270	D
2-306		377,81	342	296 (dec.)	D

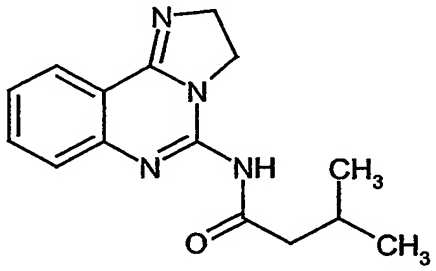
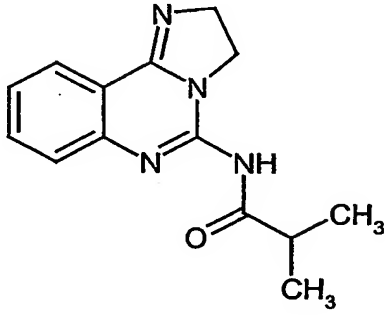
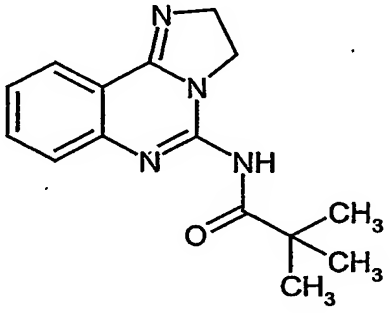
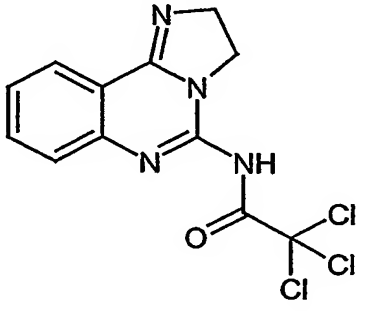
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-307		298,33	299	219 (dec.)	C
2-308		380,84	345	344 (dec.)	B
2-309		440,43	441	250-253	D
2-310		445,36	332	252 (dec.)	B

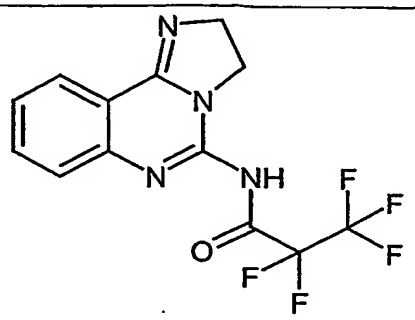
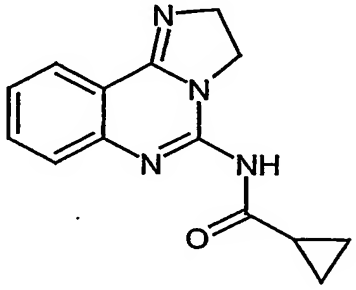
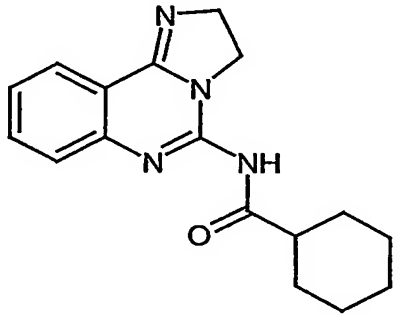
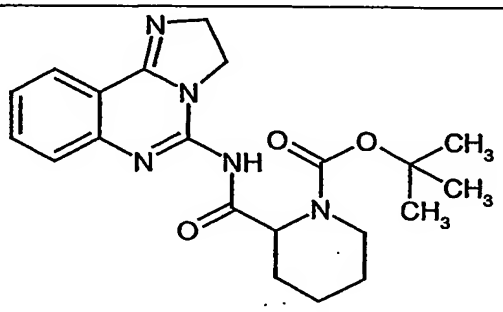
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-311		373,42	374	202-203	D
2-312		347,40	348	303-305	D
2-313		383,86	348	314 (dec.)	C
2-314		343,39	344	259 - 260	D

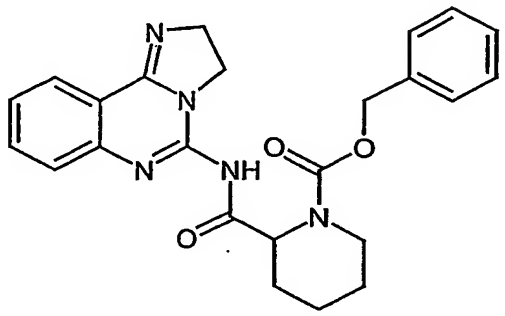
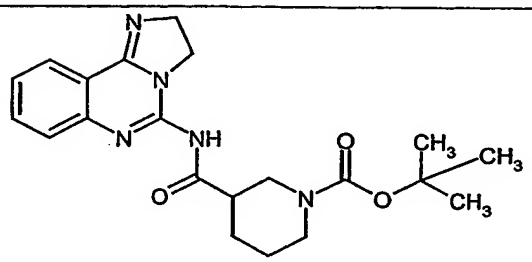
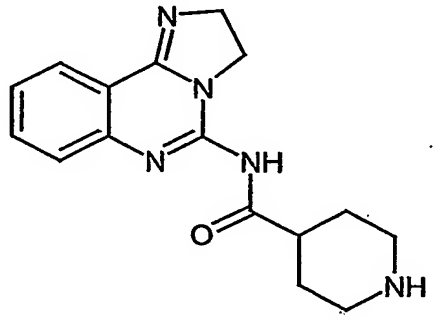
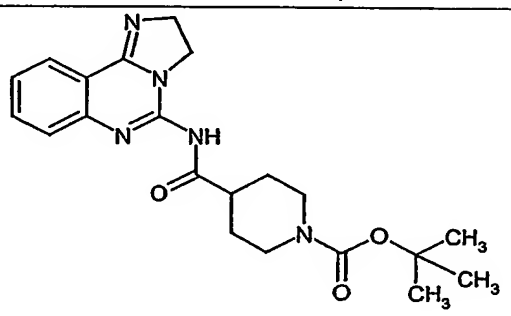
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-315		343,39	344	288 - 289	D
2-316		341,38	342	263 - 264	D
2-317		377,84	342	319 (dec.)	B
2-318		377,84	342	316 (dec.)	D

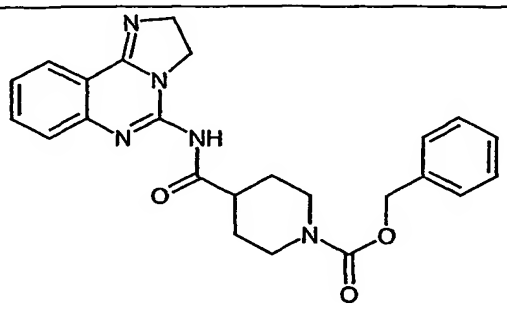
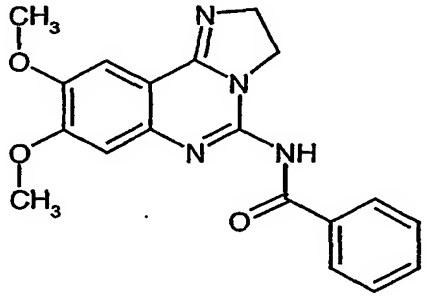
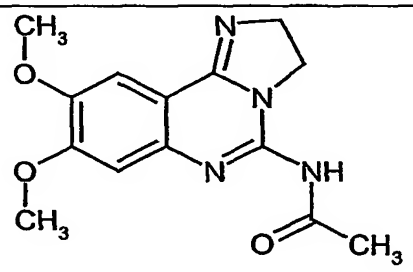
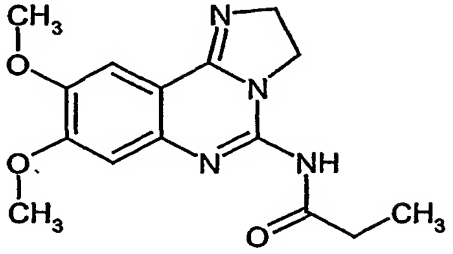
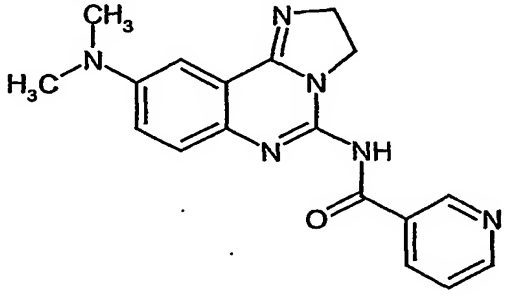
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-319		374,43	375	260 - 261	D
2-320		410,89	375	310 (dec.)	D
2-321		374,43	375	281 (dec.)	D
2-322		410,89	375	335 (dec.)	D
2-323		334,38	335	167 - 168	D

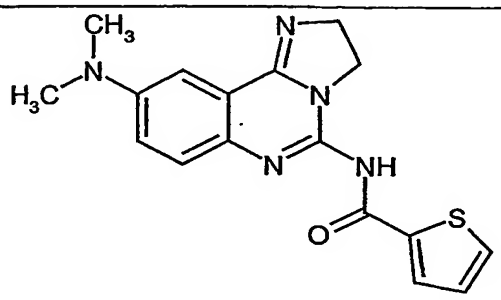
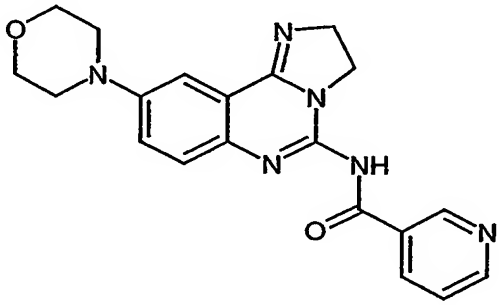
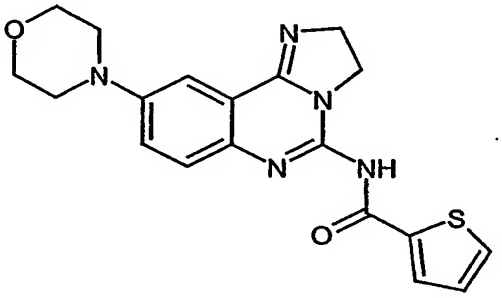
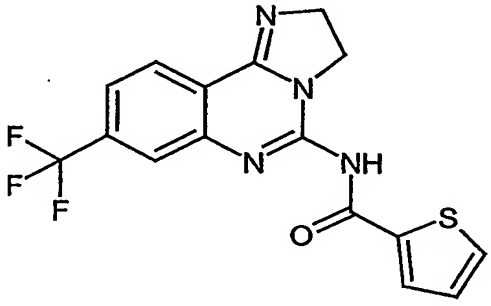
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-324		310,38	311	122 - 123	D
2-325		320,35	321	149 - 150	D
2-326		228,26	229	189	D
2-327		242,28	243	amorphous	D
2-328		256,31	257	121-122	D

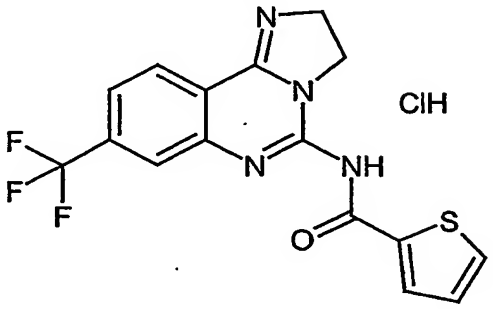
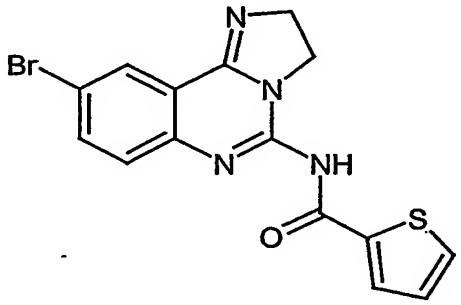
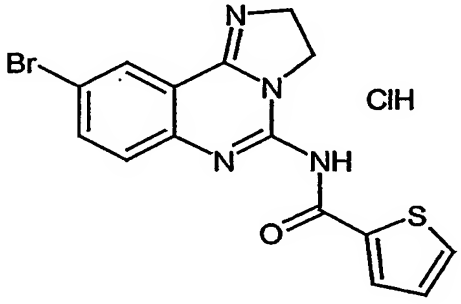
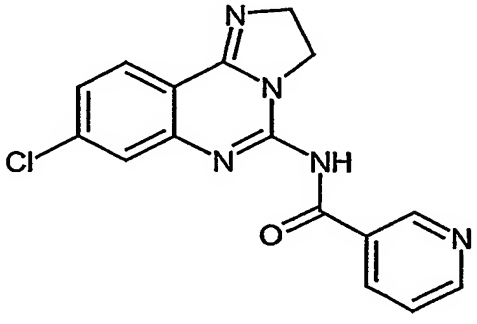
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-329		270,34	271	154 (dec.)	D
2-330		256,31	257	104-105	D
2-331		270,34	271	135-136	D
2-332		331,59	331	194 (dec.)	C

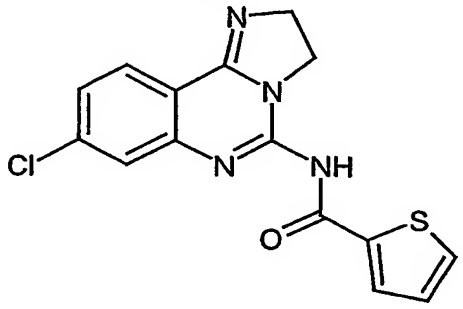
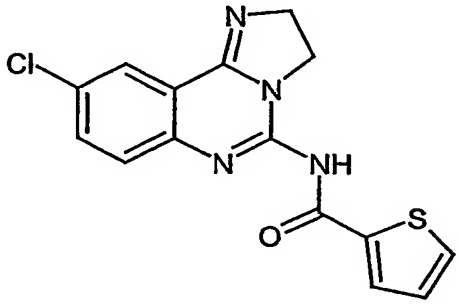
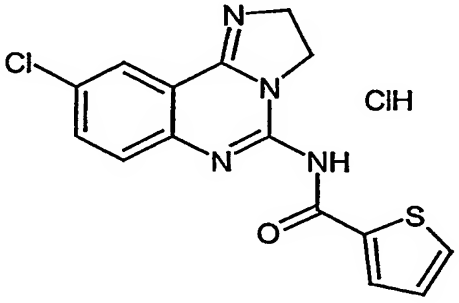
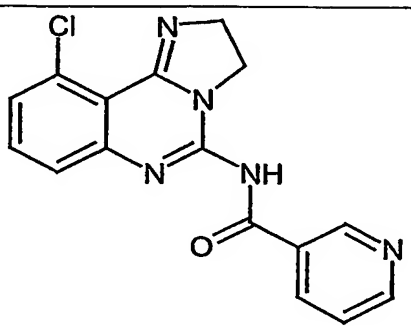
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-333		332,23	333	210-211	D
2-334		254,29	255	164 - 165	D
2-335		296,38	297	170-172	D
2-336		397,48	398	amorphous	D

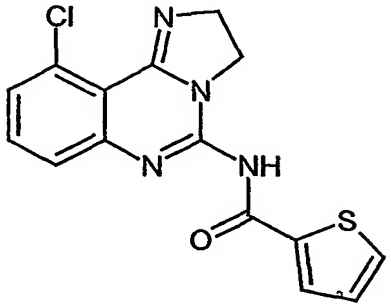
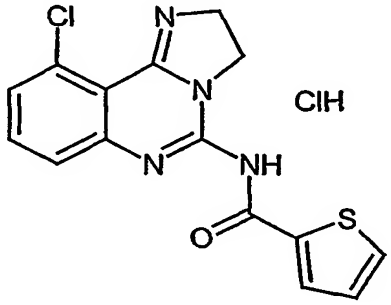
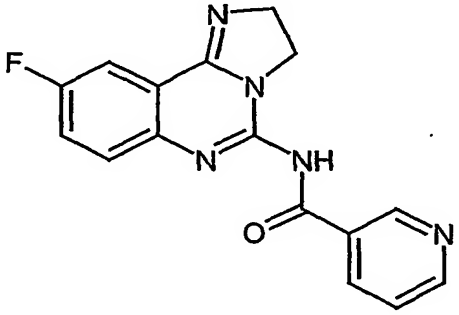
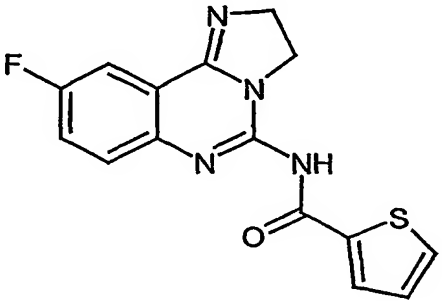
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-337		431,50	432	119 - 120	D
2-338		397,48	398	147 - 148	D
2-339		297,36	298	179 - 180	D
2-340		397,48	398	amorphous	D

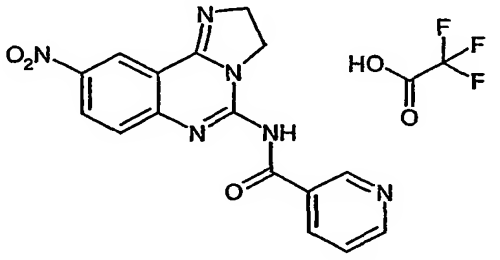
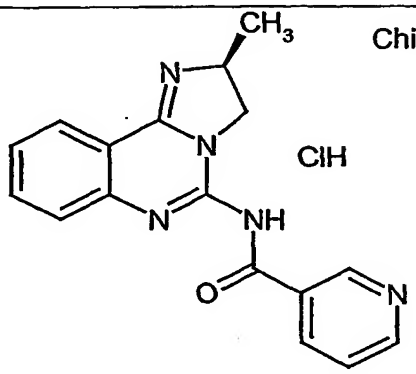
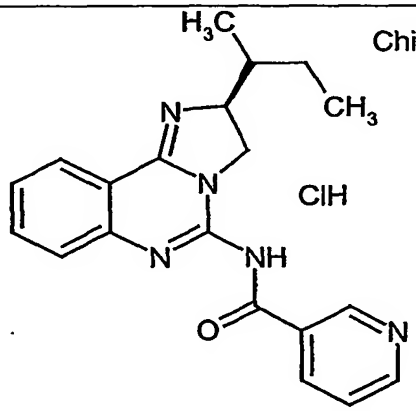
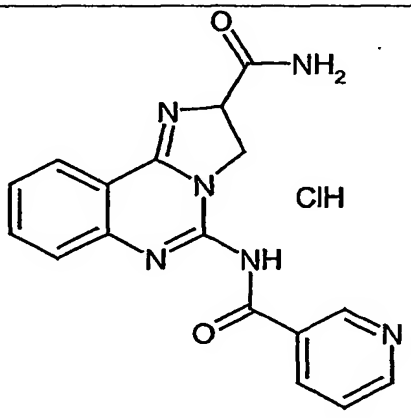
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-341		431,50	432	111 - 112	D
2-342		350,38	351	amorphous	C
2-343		288,31	289	240-241	D
2-344		302,34	303	224-225	D
2-345		334,38	335	269	C

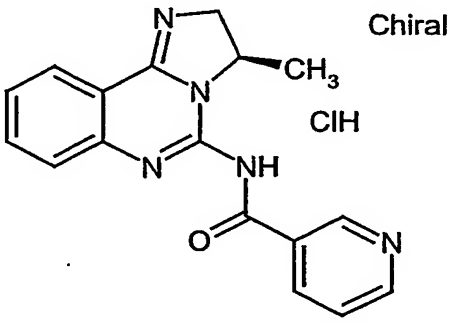
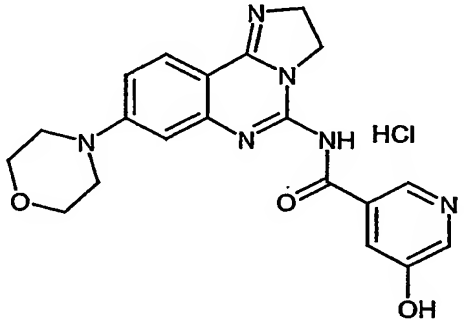
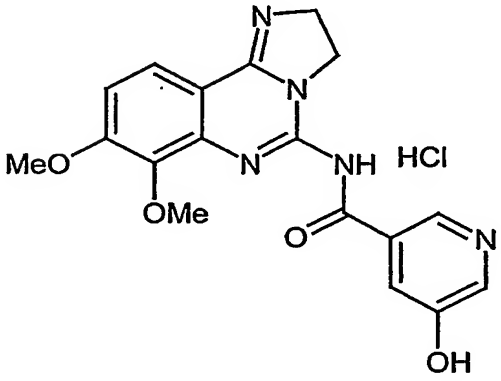
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-346		339,42	340	272	D
2-347		376,42	377	244	D
2-348		381,46	382	124	D
2-349		364,35	365	226	B

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-350		400,81	365	292	C
2-351		375,25	376	232	D
2-352		411,71	376	275	C
2-353		325,76	326	254	B

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-354		330,80	331	228	C
2-355		330,80	331	174	C
2-356		367,26	331	276	B
2-357		325,76	326	243	C

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-358		330,80	331	233	D
2-359		367,26	331	227	C
2-360		309,31	310	242	C
2-361		314,34	214	315	C

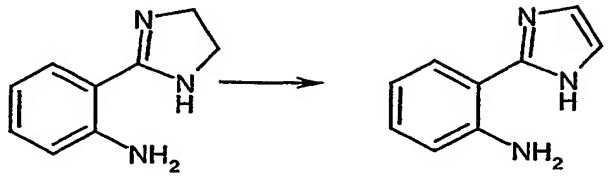
Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-362		450,34	336	224	C
2-363		341,80	306	204(dec.)	D
2-364		383,88	348	230-240	D
2-365		370,80	335	274(dec.)	D

Ex. No.	Structure	MW	MASS	mp / °C	in vitro PI3K-gamma
2-366		341,80	306	270(dec.)	D
2-367		428,88	398	273-274	A
2-368		403,83	368	240(dec.)	A

Example 3-1:

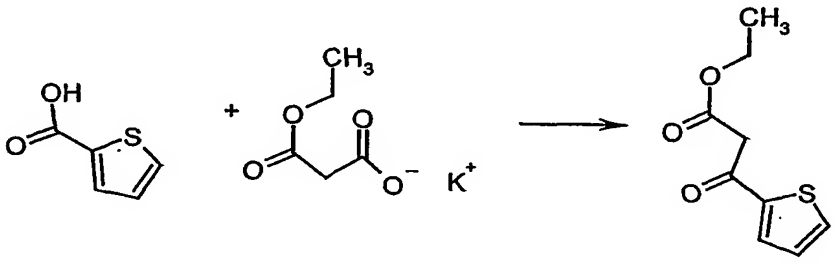
(*Z*)-2-Imidazo[1,2-c]quinazolin-5-yl-1-(2-thienyl)ethenol

(1) 2-(*1H*-Imidazol-2-yl)aniline



A mixture of 2-(4,5-dihydro-*1H*-imidazol-2-yl)aniline hydrobromide (50.0 mg, 0.207 mmol) and manganese dioxide (170 mg, 1.96 mmol) in *N,N'*-dimethylpropylenurea (2.0 mL) was heated at 150. (bath temp.). After 1 hour, the reaction mixture was cooled to room temperature, poured into a solution of hydroxylamine hydrochloride (0.5 g) in water (50 mL), and the resulting mixture was extracted with ethyl acetate. The separated organic layer was washed with brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure. The crude residue was triturated with isopropylether, and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin layer chromatography (silica-gel, ethyl acetate as the eluent) to give 2-(1H-imidazol-2-yl)aniline (20 mg, 61% yield).

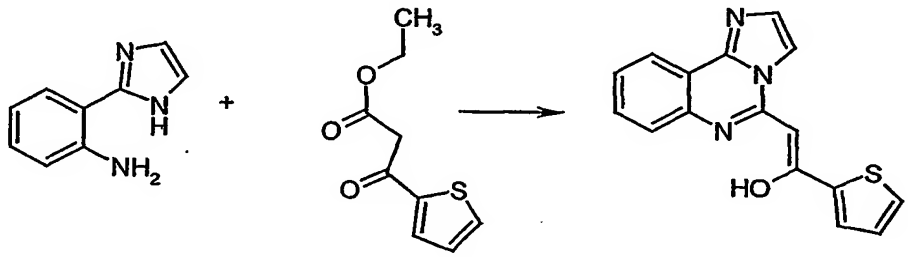
(2) Ethyl 3-oxo-3-(2-thienyl)propanoate



To a suspension of 2-thiophenecarboxylic acid (6.48 g, 50.57 mmol) in tetrahydrofurane (100 ml) at 5. was added 1,1'-Carbonyldiimidazole (8.61 g,

53.09 mmol) by portions. The mixture was allowed to warm to room temperature, and the stirring was continued for 1 hour. The reaction mixture was added into a suspension mixture of magnesium chloride (4.86 g, 51.07 mmol) and pottasium 3-ethoxy-3-oxopropanoate (12.91 g, 75.85 mmol) in tetrahydrofurane (50 ml). After being stirred at 50. for 2 hours and at room temperature overnight, the reaction mixture was poured into water ,and then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (ethyl acetate/ hexane, 15/85) to give ethyl 3-oxo-3-(2-thienyl)propanoate (7.83 g, 78% yield) as a yellow oil.

(3) (*Z*)-2-Imidazo[1,2-c]quinazolin-5-yl-1-(2-thienyl)ethenol



A mixture of 2-(1*H*-imidazol-2-yl)aniline (60.0 mg, 0.38 mmol), ethyl3-oxo-3-(2-thienyl)propanoate (74.7 mg, 0.38 mmol) and p-tolenesulfonicacid monohydrate (36.1 mg, 0.19 mmol) in toluene (30 ml) was heated at reflux for 2 hours. After cooling to room temperature, the reaction mixture was poured into aqueous saturate $NaHCO_3$ solution, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica-gel (ethyl acetate/ hexane, 2/3 - 1/1) to give (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol (37.0 mg, 33% yeild) as a yellow powder.

Melting point: 128°C

Mass spectrometry: 294

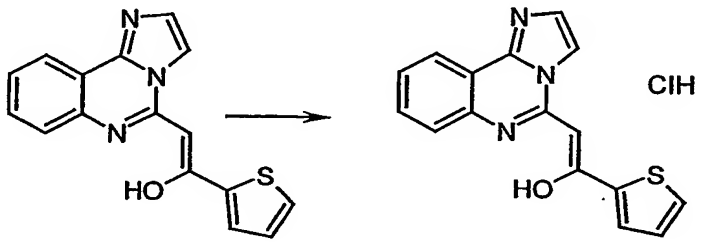
In vitro PI3K-β inhibitory activity:

In vitro PI3K-γ inhibitory activity: D

^{1}H-NMR (300 MHz, CDCl3): d 6.11 (1H, s), 7.16 (1H, dd, J = 3.8, 4.9 Hz), 7.34 - 7.41 (2H, m), 7.53 - 7.60 (3H, m), 7.64 (1H, d, J = 1.7 Hz), 7.73 (1H, dd, J = 1.1, 3.8 Hz), 8.34 (1H, dd, J = 0.9, 7.8 Hz), 14.70 (1H, bs).

Example 3-2

(*Z*)-2-Imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol hydrochloride



To a solution of (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol (0.06 g, 0.07 mmol) in chloroform (1.0 ml) was added a 4N solution of HCl in 1,4-dioxane (0.5 ml). The mixture was diluted with ethyl ether, and the resulting precipitate was collected by filtration, washed with ethyl ether, and dried under reduced pressure to give (*Z*)-2-imidazo[1,2-*c*]quinazolin-5-yl-1-(2-thienyl)ethenol hydrochloride (0.07 g, quantative) as a yellow solid.

Melting point: 263°C (decomposition)

Mass spectrometry: 294

In vitro PI3K-β inhibitory activity:

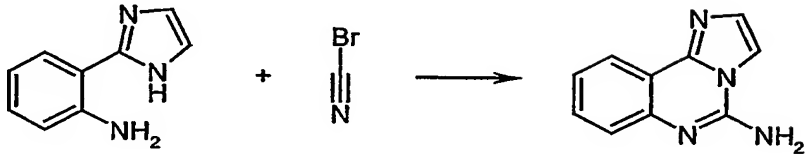
In vitro PI3K-γ inhibitory activity: D

^{1}H-NMR (300 MHz, DMSO-d6): δ 6.79 (1H, s), 7.28 (1H, dd, J = 3.8, 4.9 Hz), 7.45 (1H, t, J = 7.0 Hz), 7.66 - 7.77 (2H, m), 7.82 (1H, d, 1.7), 7.91 (1H, dd, J = 1.1, 5.0 Hz), 8.17 (1H, dd, J = 1.1, 3.8 Hz), 8.30 (1H, dd, J = 1.0, 8.0 Hz), 8.62 (1H, d, J = 1.7 Hz), 14.36 (1H, br).

Example 4-1:

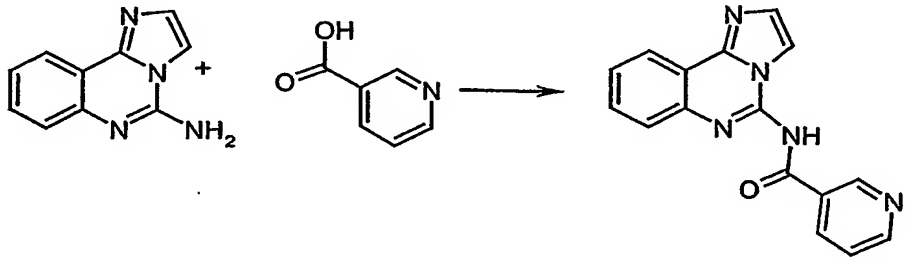
N-Imidazo[1,2-*c*]quinazolin-5-ylnicotinamide

(1) Imidazo[1,2-c]quinazolin-5-amine



To a solution of 2-(1*H*-imidazol-2-yl)aniline (0.06 g. 0.38 mmol) in methanol (3 ml) was added cyanogen bromide (0.05 g, 0.45 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was poured into water, and the resulting precipitate was collected by filtration, washed with acetone, and dried under reduced pressure to give imidazo[1,2-*c*]quinazolin-5-amine hydrobromide (0.06 g, 61% yield) as a white solid.

(2) *N*-Imidazo[1,2-*c*]quinazolin-5-ylnicotinamide



To a mixture of imidazo[1,2-*c*]quinazolin-5-amine hydrobromide (93 mg, 0.35 mmol) and nicotinic acid (124 mg, 1.01 mmol) and DMF (2.5 ml) at room temperature was added benzotriazole-l-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (525 mg, 1.01 mmol) followed by *N,N*-diisopropylethyl amine (0.264 ml, 1.51 mmol), and the mixture was stirred at 80 . for 6 hours. After cooling to room

temperature, the reaction mixture was poured into aqueous saturated $NaHCO_3$ solution. The resulting precipitate was collected by filtration, washed with acetone, and dried under reduced pressure to give *N*-imidazo[1,2-c]quinazolin-5-ylnicotinamide (40 mg, 39% yield) as a white solid.

Melting point: 223-224 °C (decomposition)

Mass spectrometry: 290

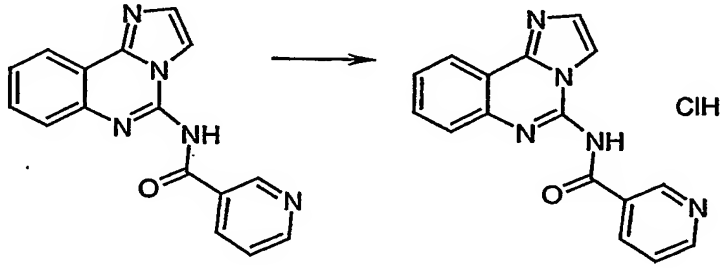
In vitro PI3K-β inhibitory activity:

In vitro PI3K-γ inhibitory activity: C

^{1}H-NMR (300 MHz, DMSO-d6): d 7.53 - 7.62 (3 H , m), 7.70 (1H, t, J = 7.34 Hz), 8.00 (1H, d, J = 8.10 Hz), 8.30 (1H, d, J = 7.91 Hz), 8.44 (1H, s), 8.63 (1H, d, J = 7.72 Hz), 8.81 (1H, dd, J = 1.5, 4.7 Hz), 9.49 (1H, s), 13.49 (1H, br).

Example 4-2

N-Imidazo[1,2-*c*]quinazolin-5-ylnicotinamide hydrochloride



To a solution of *N*-imidazo[1,2-c]quinazolin-5-ylnicotinamide (40 mg, 0.14 mmol) in methanol (20 ml) was added a 4N solution of HCl in 1,4-dioxane (0.5 ml). The mixture was concentrated under reduced pressure. The resulting solid was collected by filtration, washed with tetrahydrofurane and dried under reduced pressure to give *N*-imidazo[1,2-c]quinazolin-5-ylnicotinamide hydrochloride (40 mg, 89% yield) as a white solid.

Melting point: 228 °C (decomposition)

Mass spectrometry: 290

In vitro PI3K-β inhibitory activity:

In vitro PI3K-γ inhibitory activity: C

^{1}H-NMR (300 MHz, DMSO-d6): δ 7.60 (2H, br), 7.65 (1H, t, J = 7.5 Hz), 7.82 (1H, dd, J = 7.3, 8.1 Hz), 7.92 (1H, s), 8.02 (1H, dd, J = 5.5, 7.9 Hz), 8.54 (1H, d, J = 8.3 Hz), 8.73 (1H, s), 9.02 (1H, dd, J = 1.3, 5.3 Hz), 9.07 (1H, d, J = 7.53 Hz), 9.67 (1H, s).

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